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Systemic Review

Beginning of meta-analysis in medical literature and its progression

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Abstract

Background: Meta-analysis is an epidemiological, recognized, quantifiable study design that helps in systematical evaluation of earlier research studies to originate conclusions indicative of the body of research. This paper provides an overview to meta-analysis and to highlight its rationales and also over-all considerations related to meta-analysis. This article emphasizes on methods that are used in order to produce a demanding meta-analysis including various facets of staging and understandings of meta-analysis are deliberated.

Methodology: A Systematic literature was conducted from 1990 till 31st December 2017, utilizing PubMed, Web of science, Scopus and Embase using a single keyword "meta-analysis in medicine". We made 5 groups on the basis of years and the variation in the number of articles (meta-analyses) published.

Results: One of the critical outcomes of the meta-analysis study result is its heterogeneity or variability examination. Our results showed that the number of meta-analysis published in the recent years has excelled rapidly in comparison to the previous rate i.e. 3294 meta-analyses were published back in 1990-1995, which increased to 7863 in 1996-2000, 18044 for the year 2002-2007, 44965 articles in 2008-2013 and 76135 in 2014-2017.

Conclusion: Meta-analysis results in the detailed and accurate assessment of the consequences of various treatments, different risk factors for any particular or specific diseases or some other outcomes, other than individual research contributing to joint analysis. Thoroughly conducted meta-analyses can be a useful tool in evidence-based medicine. The needs of integrating outcomes from several studies confirm that meta-analytic research is necessary and the vast literature based on newly generated researches contribute highly in conduct of this research achievable.

Keywords

Meta-Analysis, Heterogeneity, Evidence-Based Medicine, Sorts of Meta-Analysis Bias, Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)

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Introduction

Essential research queries were considered by diverse research groups under various conditions usually more than once. Collectively, in many cases the results of these various small researches related to the same issue are inconsistent and different which increases the difficulties in clinical decision-making[1]. The requirement to reach decisions disturbing clinical practices nurtured drive towards "evidence-based medicine"[2] that can be well-defined as a systematic and quantifiable, specifically experimental approach in attaining medical information. For that reason, meta-analysis is considered as an arithmetical process resulting in integrated results of numerous independent researches and thus plays a fundamental part in evidence-based medicine[3].

Indeed, according to the evidence pyramid, clinical data should be placed as per freedom strength from numerous preferences overwhelmed medical research, meta-analyses are positioned at the top[4]. Whereas, case reports, case series, laboratory studies or animal research exhibits less clinical value in terms of proof, are placed at the bottom respectively.

Meta-analysis was less common at the beginning of medical literature till late 90's however since then, a huge advancement in the research world has been observed and the progress of meta-analysis is increasing over time (Figure 1). Additionally, meta-analyses are the most repeatedly cited practice in clinical research[5].

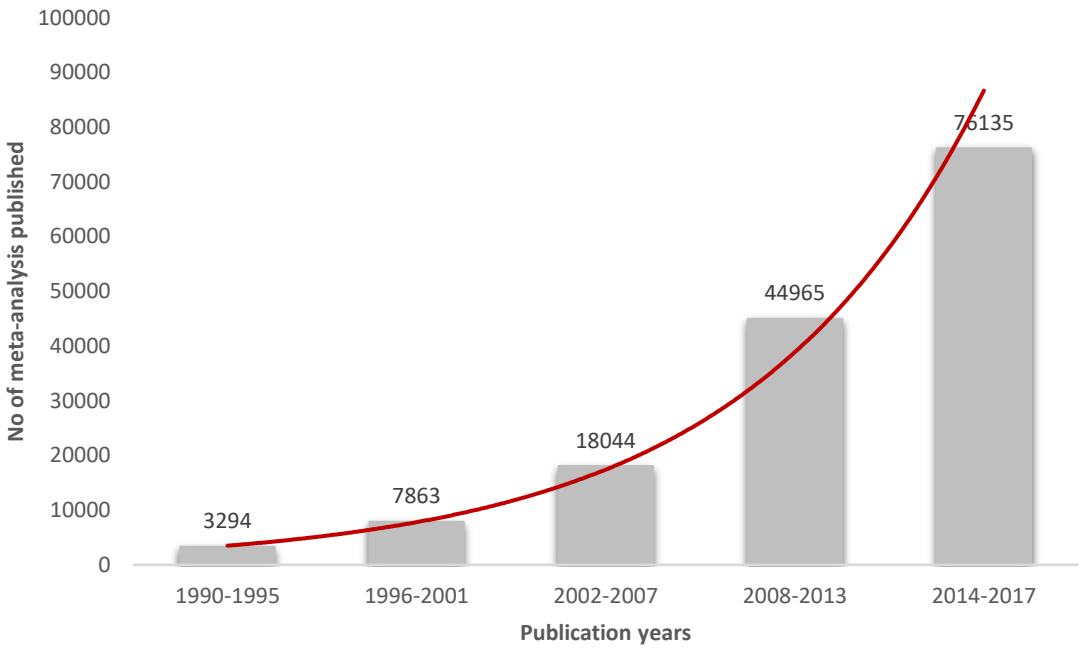


Figure 1: Evolution of meta-analyses published since 1990-2017 (Results from Medline search using the keyword "Meta-analysis").

Usually, but not mandatory, randomized controlled trials (RCT) are preferred during meta-analysis[6]. Observing heterogeneity of study groups and specifying the responses may lead to effective additional treatment or amendments in management[7]. Indeed it's the most essential task in meta-analysis[7]. The Cochrane Collaboration is considered as the pioneer and long lasting and mostly demanded methods in this field[8]. The most important contributions consist of protocol development, providing structure not only for literature search methods but also for new and comprehensive diagnostic and analytic approaches for assessing the productivity of meta-analyses[9]. Furthermore, Preferred Reporting Items for Systematic reviews and Meta-analyses (PRISMA) is another useful guide in improving meta-analyses and systematic reviews reports and it is the PRISMA report that replaces QUOROM (Quality of Reporting of Meta-analyses) statement[10&11].

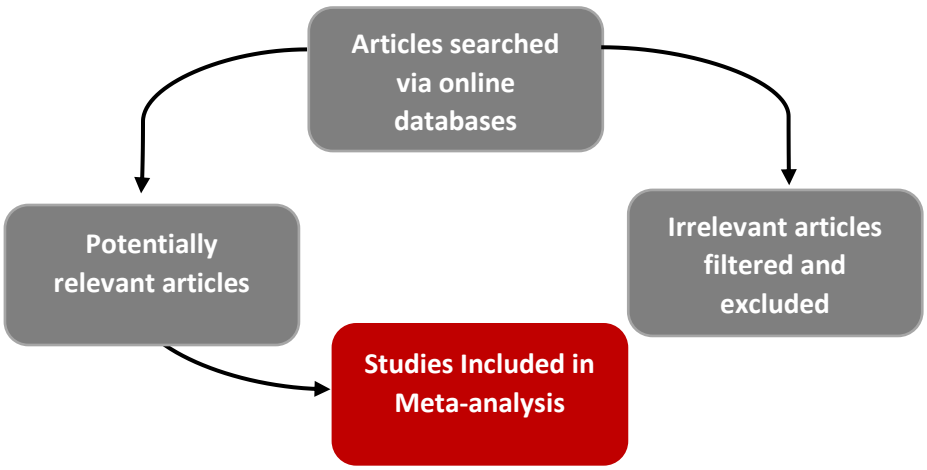
Meta-analysis is used to reveal and to evaluate the strength of evidence existing on any specific disease along with its treatment[12]. Generally, one intention is in the direction of concluding that is there any existing effect or not; one more intention is in the direction of concluding that the existing effect is good or bad[12]. The outcomes of meta-analysis may improve the accuracy of estimations of effects, provide answers to questions not sit for by individual researches, resolve disagreements rising from seemingly inconsistent studies and to create a new hypothesis. In general, the consideration of heterogeneity is dynamic in the development of new hypothesis[12].

Inclusion/exclusion criterions

Exclusion or inclusion conditions along with the probability of bias studies, selected aimed at meta-analysis are mainly grounded upon inclusion conditions. For distinct hypotheses that have to be investigated, there should be individual defined selection criterions respectively[12]. Ideally, inclusion conditions are defined no later than early development period of studies protocols[12]. The reason for the study selection conditions that have to be used should be undoubtedly stated[13]. In an ideal situation, every randomized subject in each and every study must satisfy every trial selection criteria, fulfilling the trial procedures totally and also give whole and accurate data. Some experimental studies had revealed that under certain methodological conditions, for instance bad concealment of treatments distribution or lack of blind studies misrepresents effects of treatment[12].

If any study is omitted from the meta-analysis, proper reasoning for elimination must be given for every individual research that has to be excluded. Generally, more than one evaluator can independently choose excluded or included studies, with definite worksheet and method which has to follow in case of disagreement by any of the inspectors[8]. Before evaluating study quality, development of data forms and quality assessment protocol is mandatory. The purpose is to lessen the risk of bias in the estimation of effects. That is why most studies remain incomplete due to lack of treatment failures, protocol failures or some other related reasons[13]. On the other hand, subjects and studies that are missing can give important evidences. For a most appropriate investigation that has to be undertaken, getting each and every related randomized trial data is mandatory[14]. There are a number of studies in medicine that discusses the missing trial's importance in relation to the understanding of intervention studies[13&14].

Stepwise inclusion and exclusion of articles in meta-analysis



Good Quality Studies include:

- Study Design
- Comprehensive method
- Information used for subjects
- Randomization
- Well-defined Eligibility conditions
- Outcomes measuring techniques

Literature search, Citation and Online databases

▪ As per PRISMA statement, a meta-analysis should indicate a clear statement of queries being addressed with reference to contributors, interferences, associations, conclusions and study designs (PICO: Patient, problem or population; intervention; comparison, control or comparator; outcome)[10].

▪ The most important task is to find entire related studies through electronic databanks includes Scirus, Science Direct, Google Scholar, PubMed, and ISI Web of Knowledge etc.

▪ PRISMA declaration mentions a comprehensive digital search plan for at least any one foremost database that has to be presented[11]. Database search must be improved using the printed search of reference archived resources i.e. libraries for related conference reports, abstracts, articles and books.

▪ Citations of reference cross-checking, review articles, and communicating with scientists through email etc. working in the related fields are the main ways used to deliver an inclusive and wide-range search[11].

▪ Individually it is not possible to find all full articles on any issue. More or less all researches might not be published, while those published may not be included in the directory of the computer-search engine. Most beneficial bases can be clinical trial registers for example, the National Library of Medicine's Web-site (ClinicalTrials.gov)[11].

▪ The analyses must try to be subtle, i.e. to say, try to get related studies as more as possible with the aim of minimizing bias and well-organized[12].

▪ The publication language might also be responsible for creating trouble; therefore it is essential to overwhelm this trouble, as long as the considered populaces are related to the established hypothesis.

Statistical/arithmetical analysis

Commonly used measures of effects aimed at oppositional data are the odds ratio and relative risk (also known as risk ratio), while for continuous data the dominant method used is standardized mean difference (SMD) estimation[15]. Ways and means for subsequential findings analysis are relatively specific to meta-analysis, which includes sensitivity analysis, assessment of publication bias and heterogeneity exploration[15].

The weighting of studies should be allowed in all the methods being used. The weighting idea reveals evidence significance for individual

studies. Commonly, the inverse of variance shows weighting of studies[15]. Therefore it is necessary to distinguish between smaller and well-conducted studies. This is due to the fact that smaller studies add less in assessments of total effects. On the other hand, well-conducted study with accurate variation measurements and confounding causes contributed more[15].

Consistency assessment/ heterogeneity

The ultimate advantage in conducting meta-analysis is to observe bases of heterogeneity, whether it exists or not, amongst studies. In case of heterogeneity presence, the summary size should be construed attentively[16]. Just in case of the existence of heterogeneity, whether or not and how to simplify results, is a most repeatedly asked question. Considerate causes of heterogeneity will lead to the additionally effective pointing of inhibition and treatment approaches that ultimately results in new identifiable research topics. Identifying significant factors is an important section of the strategy during meta-analysis conduct[9].

To fully recognize variability essence, it is essential to discriminate the two heterogeneity bases i.e. clinical diversity and methodological diversity[9]. Clinical diversity includes inconsistency in the contributors, interferences, and study outcomes while different study designs and risks of biasness are considered as methodological diversities[9]. Moreover, variations in the interventional effects that are being assessed amongst the differentiated studies are known to be statistical heterogeneity which can be a result of either methodological or clinical diversity or both of these, amongst the cases[9]. Generally, arithmetical heterogeneity is solely mentioned as heterogeneity in the literature. Meta-analyses scope broadly determines the range of studies involved in a review can vary[9]. For appropriate conduct of meta-analysis, the group of studies should be adequately homogeneous regarding the involvement of participants, interferences and consequences to offer a significant summary. But, it is more applicable to prefer comprehensive perception in meta-analysis than a clinical trial alone.

Usually, the discrepancy between k trials is measured by chi-squared ($\chi 2$) heterogeneity test thru degrees of freedom k-1, known as Cochran's Q statistic[17]. But the disadvantage of this test is that it has comparatively reduced power of detecting heterogeneity amongst small trials quantities[17]. Therefore, generally 0.10 α-level should be preferred for testing hypothesis[17].

Additionally, results heterogeneity amongst trials is better measured via I_2 inconsistency index that defines the fraction of entire deviation across the studies. Doubtful intervals of I 2 (dependent on k and Q) can be calculated through the way defined by Higgins and Thompson[15]. I 2 negative values should be set equals to 0, so I_2 must lie in-between 0 and 100%. >75% value can be considered as substantial heterogeneity[18].

Providing that several steps must be taken under consideration for investigation of the causes in order to evaluate numerous possible sources of heterogeneity amongst the data. For desirable examination of data in identifying sources of heterogeneity and for preceding step in the production of models exhibiting a reduced level of heterogeneity, random-effect representations are suitable[18]. Regardless of heterogeneity in various responses, if each and every study exhibiting a positive point way including that the combined confidence interval did not contain 0, most probably it wouldn't be reasonable to draw a conclusion that there wasn't any positive effect, as long as appropriate subject and studies quantities were there[18]. The pertinence of point estimation of effect is considerably high in the inquiry. By means meta-regression and subgroup analysis, one can investigate the causes of heterogeneity.

The meta-regression method uses regression analysis in order to define the impact of certain variables.

Results synthesis

The studies included in the meta-analysis are determined on the basis of PRISMA 2009[10].

It helps to identify the relevant studies to be included/excluded, and if excluded, what are the reasons for its exclusion[19]. Generally, meta-analysis results must be shown as a forest plot, where every individual study must be presented with effect size using confidence interval 95% correspondingly (Figure 2)[11].

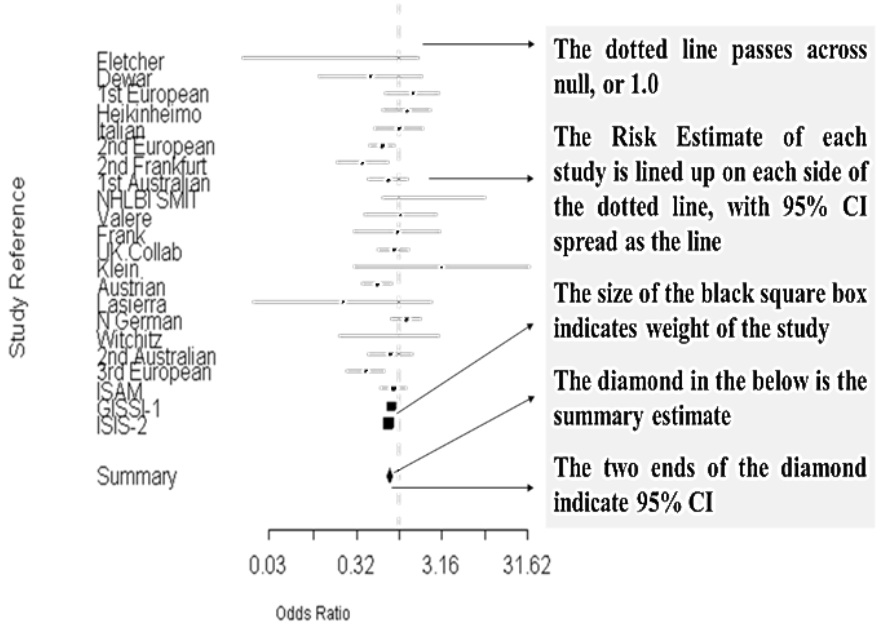


Figure 2: Forest plot description used in the meta-analysis

The combined effects along with a 95% confidence interval should be displayed at the bottommost matching line under "Overall". Figure 2, right section displays a graphical representation of cumulative meta-analysis, where data enters uninterruptedly, usually within chronological appearance sequence[20&21]. This type of cumulative meta-analysis may retrospectively identify the point of time as soon as the treatment outcome first reaches conventional significance points. Cumulative meta-analysis is considered as convincing means to observe tendencies within the progression of summaries - effected size, along with assessing the influence of specific studies on overall decisions.

Categories of Biasness

Publication Biasness

To study, each and every meta-analysis results as an indication or sign of publication bias is mandatory. A guesstimate of expected publication bias size within reviews as well as a method to deal with biasness can inherent to the conducts of numerous meta-analyses[22]. Numeral approaches are developed with the purpose of offering publication bias assessments, of which the funnel plot is more commonly used[23]. It offers a representative potential of bias assessment, which was established by Light and Pillemer[22] and was firstly deliberated by Egger with his colleagues[23&24]. The funnel plot is basically a

treatment effects scatterplot contrary to the degree of study size. In case of absence of publication bias, this plot may be anticipated to possess symmetric upright funnel shape.

In studies with lack of publication bias for example, larger studies i.e. having lesser standard errors, tends to gather narrowly at the point estimate[24]. As soon as studies turn into less detailed, for instance in small trials i.e. having a greater standard error, their results are predictable of extra variables that scatters to both sides. While the shorter, less detailed studies scatter equally to both sides of point estimates of effects, also that it seems to be symmetrical just like inverted funnel-plot, displaying lack of evidences of publication biasness[24&25].

Yet it is not necessary that the funnel plots asymmetry is only due to publication bias, it might be a result of clinical heterogeneity between studies. Variation in exposure or control of subjects to effect modifiers or confounders, or else methodological heterogeneity amongst studies can be reasons for clinical heterogeneity[23]. There are some statistical assessments used in order to identify asymmetric funnel plot; such as Begg's rank correlation test[26] and Egger's linear regression test[23] however, these are very rarely used. Still, the funnel plot exhibits many complications[27]. A funnel plot might be changed somewhat vividly conditionally by Y-axis scale, in case of trial size or inverse square error[25].

Selective Reporting

The selective reporting bias occurs if there is incomplete or inadequate reporting in published articles. This type of bias has been shown by empirical studies that can be of substantial significance whenever published studies have to match with its protocol. In addition, current evidence recommends that discriminating reporting may be a concern in safety effects and also that the problems reporting within the clinical trial is quiet negligible[28]. Hence, that may be infeasible aiming to practice quantifiable unbiased evidence for destructions in meta-analyses execution and based on this creating therapeutic decisions.

Time Lag Biasness

The time lag bias rises as a result when the published studies with remarkable results can be published prior to those having normal conclusions[28].

Language Biasness

While conducting meta-analyses, the language bias emerges with the exclusion of clinical trials conveyed in languages except for English. It also reduces the accuracy of combined assessments of treatment effects. To overcome this type of biasness, clinical trials having statistically substantial results should be published in English[29].

Development of meta-analytic network

A standard meta-analysis relates 2 actions whereas meta-analysis network also known as meta-analysis based on multiple treatments provides estimations for multiple management regimens even if direct associations might be inaccessible by indirect links[30]. For instance, a primary trial relates drug I to drug 2 and another trial compares drug 2 to drug 3 using the same population. Now assume that during the first trial, drug I was proven to have a better effect then drug 2. While during the second trial, drug 2 was found to be equally effective as drug 3. So using these evidences, network analysis can statistically declare that drug I exhibits a better effect than drug 3, keeping in mind the specific patient populace. As drug I work more efficiently than drug 2, also drug 2 is comparably same as drug 3, so drug I also possess better efficacy than drug 3 although it wasn't examined against drug 3 directly.

For giving brief information about the performance of the prognostic and diagnostic test, meta-analysis is also useful. But, studies that estimate the accurateness of investigations possess a unique design demanding different conditions to suitably evaluating the studies qualities and the possible reasons for biasness. With the emerging trends, various methods for summarizing outcomes of prognostic and diagnostic tests results have been recommended[31-33].

The concept of meta-analysis is not new anymore in medicine. Many meta-analyses have been accompanied at the same time for similar medical topics by various researchers at different places. Currently, there exists a new technique to associate the outcomes of many dissimilar meta-analyses, called meta-epidemiological studies, for the purpose of evaluating risks of biasness[34].

Conclusion

A standard beginning of curative practice has been transformed using blinded, randomized, meta-analysis and multicenter clinical trials that lead to the extensively used word "evidence-based medicine". Influential in originating this modification is the Cochrane Collaboration who was responsible for creating guidelines for useful conducting meta-analyses and systematic reviews and after that, the PRISMA statement, a useful means to advance reporting of meta-analyses and systematic reviews was released. Likewise, criterions used to report and conduct observational studies meta-analysis of have been available for expanding reporting worth.

Despite having all these facts, there is not an individual study, whether it's meta-analytic or not, are responsible for the conclusive understanding of responses to risk factors influencing disease or treatment and diagnostic examinations. Even though meta-analyses methods possess discernable benefits while highlighting limits of study size, offers the chances to assess new hypothesis, includes varied populations and are additionally valued than any solo study contributes to the exploration process.

Conflicts of Interest

None.

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References

1. Stroup DF, Berlin JA, Morton SC, Olkin I, Williamson GD, Rennie D, Moher D, Becker BJ, Sipe TA, Thacker SB. Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis of Observational Studies in Epidemiology (MOOSE) group. JAMA. 2000; 283(15): 2008–2012.
2. Guyatt GH, Haynes RB, Jaeschke RZ, Cook DJ, Green L, Naylor CD, Wilson MC, Richardson WS, "Users' guides to the medical literature: XXV. Evidence-based medicine: principles for applying the users' guides to patient care." JAMA. 2000; 284(10): 1290-1296.
3. Sackett, David L. "Evidence-based medicine." Wiley StatsRef: Statistics Reference Online. 2000.
4. Haidich, Anna-Bettina. "Meta-analysis in medical research." Hippokratia 14.Suppl 1; 2010: 29–37.
5. Patsopoulos NA, Analatos AA, Ioannidis JP. Relative citation impact of various study designs in the health sciences. JAMA. 2005; 293: 2362-2366.
6. Uetani K, Nakayama T, Ikai H, Yonemoto N, Moher D. Quality of reports on

randomized controlled trials conducted in Japan: evaluation of adherence to the CONSORT statement. Intern Med. 2009; 48(5):307-313.
7. Guyatt GH, Sackett DL, Sinclair JC, Hayward R, Cook DJ, Cook RJ, Bass E, Gerstein H, Haynes B, Holbrook A, Jaeschke R. Users' guides to the medical literature: IX. A method for grading health care recommendations. Jama. 1995; 274(22):1800-1804.
8. Juni P, Altman DG, Egger M. Systematic reviews in health care: Assessing the quality of controlled clinical trials. BMJ. 2001; 323: 42–46.
9. Handbook CR, Higgins JP, Green S. Cochrane handbook for systematic reviews of interventions. Version 5.0.2. The Cochrane Collaboration. 2009.
10. Moher D, Liberati A, Tetzlaff J, Altman DG; PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. J Clin Epidemiol 2009; 62:1006-1012.
11. Liberati A., Altman DG, Tetzlaff J, Mulrow C, Gøtzsche PC, Ioannidis JP & Moher D. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. PLoS medicine. 2009; 6(7): e1000100.
12. Pildal J, Hróbjartsson A, Jorgensen KJ, Hilden J, Altman DG, Götzsche PC. Impact of allocation concealment on conclusions drawn from meta-analyses of randomized trials. Int J Epidemiol. 2007; 36(4): 847-857.
13. Chan AW, Hróbjartsson A, Haahr MT, Götzsche PC, Altman DG. Empirical evidence for selective reporting of outcomes in randomized trials: comparison of protocols to published articles. JAMA. 2004; 291(20): 2457–2465.
14. Dwan K, Altman DG, Arnaiz JA, Bloom J, Chan AW, Cronin E, Decullier E, Easterbrook PJ, Von Elm E, Gamble C, Ghersi D. Systematic review of the empirical evidence of study publication bias and outcome reporting bias. PLoS One. 2008; 3(8):e3081.
15. Higgins, John, and Steve Field. "HSRPP Conference 2012. University College Cork, Ireland Day." Int J Pharm Pract. 2012: 20(1); 1-4
16. Nikolakopoulou A, Mavridis D, Salanti G. Demystifying fixed and random effects meta-analysis. Evid Based Ment Health. 2014; 17(2) 53-57.
17. Mittlböck, M., and H. Heinzl. A simulation study comparing properties of heterogeneity measures in meta-analyses. Stat Med. 2006; 25(24): 4321-4333.
18. Higgins JP, Thompsom SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analysis. BMJ: Brit. Med. J. 2003; 327(7414): 557–560.
19. Moher D, Liberati A, Tetzlaff J, Altman DG; PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. J Clin Epidemiol 2009; 62: 1006-1012.
20. Lau J, Schmid CH, Chalmers TC. Cumulative meta-analysis of clinical trials builds evidence for exemplary medical care. J Clin Epidemiol. 1995; 48(1): 45–57.
21. Ioannidis JP, Lau J. State of the evidence: current status and prospects of meta-analysis in infectious diseases. Clin Infect Dis. 1999; 29(1): 1178–1185.
22. J. Light R, B. Pillemer D. Summing Up: The Science of Reviewing Research Harvard University Press: Cambridge, MA, 1984, xiii+ 191 pp. Educ Res. 1986; 15(8):16-17.
23. Egger M, Smith GD, Phillips AN. Meta-analysis: principles and procedures. BMJ. 1997; 315: 1533-1537.
24. Sterne JA, Egger M. Funnel plots for detecting bias in meta-analysis: guidelines on choice of axis. J Clin Epidemiol. 2001; 54(10): 1046–1045
25. Tang JL, Liu JL. Misleading funnel plot for detection of bias in meta-analysis. J Clin Epidemiol. 2000; 53(5): 477–484.

26. Begg CB, Mazumdar M. Operating characteristics of a rank correlation test for publication bias. Biometrics. 1994; 50(4): 1088-1101.
27. Deeks JJ. Systematic reviews in health care: Systematic reviews of evaluations of diagnostic and screening tests. BMJ. 2001; 323: 157–162.
28. Haidich AB, Charis B, Dardavessis T, Tirodimos I, Arvanitidou M. The quality of safety reporting in trials is still suboptimal: Survey of major general medical journals. J Clin Epidemiol. 2011; 64(2):124-135.
29. Egger M, Zellweger-Zähner T, Schneider M, Junker C, Lengeler C, Antes G. Language bias in randomised controlled trials published in English and German. Lancet. 1997; 350(9074): 326–329.
30. Lumley T. Network meta-analysis for indirect treatment comparisons. Stat Med. 2002; 21(16): 2313–2324.
31. Littenberg B, Moses LE. Estimating diagnostic accuracy from multiple conflicting reports: a new meta-analytic method. Med Decis Making. 1993; 13(4): 313–321
32. Reitsma JB, Glas AS, Rutjes AW, Scholten RJ, Bossuyt PM, Zwinderman AH. Bivariate analysis of sensitivity and specificity produces informative summary measures in diagnostic reviews. J Clin Epidemiol. 2005; 58(10): 982-990.
33. Rutter CM, Gatsonis CA. A hierarchical regression approach to meta-analysis of diagnostic test accuracy evaluations. Stat Med. 2001; 20(19): 2865–2884.
34. Wood L, Egger M, Gluud LL, Schulz KF, Jüni P, Altman DG, Gluud C, Martin RM, Wood AJ, Sterne JA. Empirical evidence of bias in treatment effect estimates in controlled trials with different interventions and outcomes: meta-epidemiological study. BMJ. 2008; 336(7644):601-605.