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A PREVIEW OF 'META-ANALYSIS' QUANTITATIVE SYNTHESIS OF THE DIVERSE STATISTICAL RESEARCH RESULTS

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***ABSTRACT**-- The Clinical Trials are being carried out across the world over various geographical areas, on diverse races & ethnics, on various economic groups, with different set of Samples, with Research Methodological differences, laden with different levels of Biases, etc., Often the Researches are repeated by different Researchers at different locations to confirm the previous Research results or to increase their precision & validity. But this Replication of the Researches is often quite difficult due to the above said diverse reasons. Subsequently thus obtained statistical results are also diverse and at times conflicting to each other. In spite of these difficulties integration of findings of different individual studies is much important. The judicious integration of analogous Research results excluding the insignificant deviations has a major role in establishing an 'Evidence Based Medicine'. Meta-analysis is a technique used to systematically merge the findings of different independent studies, using rigorous statistical methods to calculate an 'absolute' effect. This review article is primarily aimed at exploring the rationale of the Scientific Methodology – Meta-analysis.*

***Keywords**--Evidence Based Medicine, Clinical Trial, Research Reports, Research Articles, Statistical Results, Systematic Review, Meta-analysis*

I. INTRODUCTION

The Clinical Trials are being carried out across the world over various geographical areas, on diverse races & ethnics, on various economic groups, with different set of Samples, with Research Methodological differences, laden with different levels of Biases, etc., The Results of such Researches are published by means of Research Articles through various Journals. The Heterogeneity in the Trials may be of Variability in Participants, Interventions and Outcomes. The participant selection in these studies will be differing with respect to the Age group, Gender, Race, Ethnicity, Social & Economic status, Co-morbid conditions, etc., The Interventions may be varied according to the Type of Drug, its Dosage, Method of selection, Mode of application, etc., The assessment of Outcome also might be differing with the Qualitative and/or Quantitative Parameters opted in different studies. This Heterogeneity found in the trails often affect the results by a Positive or Negative skewness when we tend to integrate them. In spite of these difficulties integration of findings of different individual studies is much important as the judicious integration of analogous Research results excluding the insignificant deviations

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has a major role in establishing an 'Evidence Based Medicine'. Systematic Reviews and Meta-analysis are usually executed together, as the former deals with Qualitative and the later deals with Quantitative scientific methodologies aimed at the integration of individual findings of different Researches with careful consideration of the Heterogeneity.

II. SYSTEMATIC REVIEWS

A systematic review is a research article that identifies relevant studies, appraises their quality and summarizes their results using a scientific methodology.[3] Systematic reviews differ from traditional narrative reviews in several ways. Narrative reviews are mainly descriptive and they do not involve a systematic search process. Often they focus on a subset of studies found in an easily approachable area chosen based on availability or special preference to particular author. Thus collected narrative reviews often include selection bias.[4] But Systematic Reviews follow a defined structure to identify, evaluate and summarise all available evidences addressing a particular Research Question.[5] Systematic Reviews summaries the Results of available carefully designed healthcare studies / trials and provides a high level of evidence on the Effectiveness of Healthcare Interventions.[6]

Table 1: Major Differences between Traditional literature Review & Systematic Review [7]

	Traditional Literature Review	Systematic Review
The review question/topic	Topics may be broad in scope; the goal of the review may be to place one's own research within the existing body of knowledge, or to gather information that supports a particular viewpoint.	Starts with a well-defined research question to be answered by the review. Reviews are conducted with the aim of finding all existing evidence in an unbiased, transparent and reproducible way.
Searching for studies	Searches may be ad hoc, and based on what the author is already familiar with. Searches are not exhaustive or fully comprehensive.	Attempts are made to find all existing published and unpublished literature on the research question. The process is well-documented and reported.
Study selection	Often lack clear reasons for why studies were included or excluded from the review.	Reasons for including or excluding studies are explicit and informed by the research question.
Assessing the quality of included studies	Often do not consider study quality or potential biases in study design.	Systematically assess risk of bias of individual studies and overall quality of the evidence, including sources of heterogeneity between study results.
Synthesis of existing research	Conclusions are more qualitative and may not be based on study quality.	Base conclusion on quality of the studies, and provide recommendations for practice or to address knowledge gaps.

There is a wide utilization of Systematic reviews in the Medical Fraternity. Basically they provide a comprehensive overview of available quality evidences on the selected topic. Further they help the Researchers to identify the research gaps in the present understanding of the selected topic. On the basis of previously completed Systematic Reviews the Researchers can adopt the correct and suitable methodology for their studies so as to yield precise and valid results.[8] Thus Systematic Reviews serve as the Reference Standard for

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synthesizing evidence in health care because of their Methodological Rigor. They are used to support the development of 'Clinical Practice Guidelines' and 'Informed Clinical Decision-making'.[9] They also play a vital role in drafting the Health Policy Guidelines by Government agencies. All Systematic Reviews need not be having Meta-analysis synthesis. The detailed methodologies are out of the scope of this Review. In short Systematic Reviews are 'Qualitative Synthesis' of the available best evidences.

III. META-ANALYSIS

Meta-analysis is a research process used to systematically synthesize or merge the findings of single, independent studies, using statistical methods to calculate an overall or 'absolute' effect. [10] Meta-analysis is a set of statistical methods for combining quantitative results from multiple studies to produce an overall summary of empirical knowledge on a selected topic. It is used to analyze Central Trends & Variations in results across studies, and to correct for error and bias in a body of Research. [3,11] Simply saying Meta-analysis is a Quantitative study design used to systematically assess the results of previous researches to derive cumulative statistical conclusion. Meta-analysis need not to an-add on part of a Systematic Review always. But Mata-analysis always starts from Systematic Reviews. In general Meta-analysis can be executed by the following classical steps.

3.1. Review question

A Clinical research question is identified and based on that a valid hypothesis is proposed. PICO frame work is a well suited method to make structure a Proper & Complete Review question. PICO stands for 'Participant-Intervention-Comparator-Outcomes'.

Participants denote the included patients for the selected studies; might be particular age group patients of a particular disease or a stage of the disease; this may be further narrowed down according to our research interest.

Intervention refers to the treatment given for the patients in the selected studies; it may a new medicinal substance or improvised medicinal substance or a dose modulated medicinal substance or a new combination medicinal substance; such that the intervention is specified according to the interest of the reviewer.

Comparator is the particular mode of treatment to which the Study Intervention is compared for its effectiveness. In general but not all the times, meta-analyses are done in Randomized Controlled Trials or Quasi-experimental studies; usually they will be consisted of more than one interventional groups; study intervention and placebo or study intervention and conventional treatment or study intervention and no treatment are compared for the efficacy.

Outcomes are the possible results of the study which may be narrowly or broadly defined based on the objectives; they may be the clinical changes in health state like morbidity or mortality, improvement in clinical condition or not, worse or better, etc., Clinically relevant outcomes directly measure what is important to patients in terms of how they feel, what their function is, and whether they survive.

Apart from the above explained PICO frame work reviewers have to decide on the type of study design he or she is aimed at; interventional or observational, controlled or non controlled, blinded or open labeled, randomized or non randomized, experimental or quasi experimental, etc., [3,12,13]

3.2. Literature Search for identifying relevant studies

The relevant studies can be searched from the major Online Biomedical Bibliographic Databases like Pubmed (U.S National Library of Medicine), EMBASE (Elsevier), SCOPUS, Web of Science, Cochrane Library, Clinical Trail Registries, etc., There are various Subject specific databases available for retrieving the Bibliographic information and abstract of the articles. All these databases have their specific search strategy for retrieving the information. But a commonly suggested method is using suitable 'Boolean Operators - AND, OR, NOT' in between the Key Words in the Search Bar.[14,15]

Most of the Databases provide the facility of 'Filters' for searching. These Filters allow the reviewers to retrieve only the needed articles. Some of the common filters available are: Abstract, Full Text, Free Full Text, Human studies, Animal studies, Publication Languages, Type of Journal, Publication Period, Clinical Trials, Systematic Reviews, Meta-analysis, etc., Such that a reviewer can use the needed filters and can retrieve only the relevant articles.[16]

Some data bases provide the facility of searching using PICO frame work as Keywords; so that the reviewers can directly search with their interested strategies. This facility is seen in Pubmed[17], Cochrane[18] and EMBASE[19]. Studies have shown that PICO frame work search strategy can improve the relevancy of search results and yields high precision particularly in lager target studies.[20] Reviewer shall not end his search with this online databases alone as not all the journals are indexed in online databases; but should extend his or her search to the Offline print only journals, Books or Chapters published, Published Conference Proceedings, Completed Research Thesis or Dissertations, Government Publications, Orations or interviews of Scientists, Grey Literature, etc in the relevant field. This search process should be extended till the same results are repeated showing a saturation.[12] To avoid the personal biases in the Literature search, two blinded reviewers will start searching for the PICO Key words and share their results to the other; they will cross check the other's results; this helps in avoiding chance of biased withdrawal of any results by any of the reviewers. Duplication of articles will also be removed at this process. Usually the two reviewers will be the Researcher and the Supervisor. A log of finally selected articles will be maintained for further proceedings.

3.3. Scrutinize the obtained Literature for their utility

Not all the obtained literature by extensive search could be suited for the Study. So it is important to read the abstract of each article in complete for its relevancy with respect to the Study question, Study design, Sample design, Intended population, Intervention, Comparison, Adequacy of the Data set, Out come assessment, etc., At this process the unfit articles will be excluded by keeping a log with the reasons why they are excluded. Such that the transparency will be maintained in excluding articles from the Study.[21] Further the articles are to be chronologically arranged based on the name of the First authors and publication year. After this arrangement, the articles may be sub grouped according to the need like the level of randomization, blinding status, control type, interventional category, etc., This procedure gives the reviewer a clarity of the availability of the articles under each category.

3.4. Quality Analysis of the Literature

Quality assessment will be the next important step which is based on critical appraisal of the individual complete articles. The quality of a study may be defined as the degree to which it employs measures to minimize bias and error in its design, conduct and analysis. This includes the search for the possibility of any biases at the Selection, Intervention or outcome assessment levels and the process of Blinding adopted. Some of the specific standardized checklists are available to appraise the quality of different types of studies. Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement[22], Consolidated Standards of Reporting Trials (CONSORT)[23], Standards for Reporting Qualitative Research (SRQR)[24] and Consensus-based Clinical Case Reporting Guideline Development (The CARE Guidelines)[25] are such guidelines available. They can be utilized by the researchers for reporting the results and by the reviewers for analyzing the published study qualities.

Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) 2015 statement enhance the completeness of reporting of review protocols, facilitate the assessment of potential in systematic reviews, and hopefully strengthen the methodological quality and reliability of completed systematic reviews and mata-analysis.[26] Meta-analysis Of Observational Studies in Epidemiology (MOOSE) checklist is such a specialized guideline available.[27] These guides are usually written for supporting evidence-based practice and provide advice on appraisal of individual studies according to the nature of the clinical query, which we delineate when framing our question. A Reviewer can find any one of the many published guides for the critical appraisal of healthcare literature. The items in these guides can also be used as a basis for developing a checklist for a specific topic to perform an in-depth appraisal of the quality of each study included in a review.[3] At this level also the reports which are found to be having low quality, incomplete information, biases, etc., can be eliminated by keeping a log of the Specific Reason for each such elimination. Now at the end of this stage, what the reviewer gets is the final list of Articles to be further analyzed.

3.5. Data Extraction from the selected studies

Next key step is the retrieval of the needed data from the selected studies. It is considered to be a crucial task as this data will be utilized for Mata-analysis directly. Several data-extraction tools are available to assist reviewers but the Choice depends on resources and review complexity. Selecting the optimal tool requires balancing the upstart and maintenance effort and costs to obtain the necessary functionality for often complex projects. For Simple Reviews done at a single centre the data may be recorded even with Paper and Pen. However, inaccurate interpretation of handwritten data may create input errors when they need to be transferred to other electronic platforms for computer assisted statistical analyses procedures. The Data from larger studies can be recorded in Microsoft Excel Spreadsheets. Publication details, methodological quality, and characteristics of the patients, interventions, and outcomes can be recorded in Microsoft Excel Spreadsheets. Most of the Data Analysis software's allow the import of Data from Microsoft Excel Spreadsheets directly making it easier. Software's like RevMan have the unique function of direct data entry which can even be used for Complicated Reviews. Web based Forms and Survey software's can also be used for Simples Reviews.[28] Some of the ready to use Standardized Data Extraction Sheets are also available like Data extraction for complex meta-analysis (DECiMAL) guide for Network meta-analysis (NMA), multiple outcomes analysis and analysis combining

different types of data.[29] But it is always better for a reviewer to generate a specialized one for their review incorporating the finer data to be extracted.

3.6. Analyzing the Heterogeneity of the selected studies

Heterogeneity in meta-analysis refers to the variation in study outcomes between studies. Three types of heterogeneity can be seen in Meta-analyses:

Firstly Clinical baseline heterogeneity - These are differences between sample characteristics of the studies. For example, while one study might have included rather old people into their study, another might have recruited study participants who were mostly quite young. This can be avoided by fixing specific range inclusion and exclusion criteria.

The next is Statistical heterogeneity - This is the statistical heterogeneity reviewer can find in their collected effect size data. Such heterogeneity might be either important from a clinical standpoint (e.g., when we do not know if a treatment is very or only marginally effective because the effects vary much from study to study), or from statistical standpoint.

The other sources such as Design-related heterogeneity - may be controlled for to some extent by restricting the scope of our search for studies to certain well-defined intervention types, populations, and outcomes.[30]

In a Meta-analysis, there is an implicit assumption that the studies have come from a population that is fairly uniform across the intervention and outcomes. This may indicate one of the two issues.

The first one is that the studies that have been selected are assumed to be exhaustive and the estimates are based on the subset of evidences that are identified, so that the outcome estimate is the true association. This is the concept of Fixed effects Meta-analysis.

Alternatively, the other concept is that the studies that have been identified for the Meta-analysis constitute a sample that is part of a larger population of studies. That said, this subset of studies from that larger population is interchangeable with any other study in that wider population. Hence this set of studies is just a random sample of all possible studies. This is the notion of random effects Meta-analysis.

There are three types of commonly used Heterogeneity measures viz Cochran's Q, Higgin's & Thompson's I^2 and Tau-squared measures. At this level a reviewer should consult a Bio-statistician for the Expert Help.[31]

3.6.1 Concept of Fixed & Random Effect Models

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3.7 Estimation of Summary Effect

The summary effect estimate should be determined first by assuming both Fixed and Random effects model. Then a Forest Plot is to be created to visually inspect how the effect estimates of each individual study are distributed around a null value but also around the overall effect estimates. There are various statistical programs available to calculate effect estimate and to create Forest Plots like RevMan.[33]

An effect size is the quantitative measure of the magnitude of a phenomenon calculated from a sample of data compared to the value of a parameter of a Hypothetical statistical population.[34] Examples of effect sizes include the correlation between two variables, the regression coefficient in a regression, the mean difference or the risk of a particular event.[35]

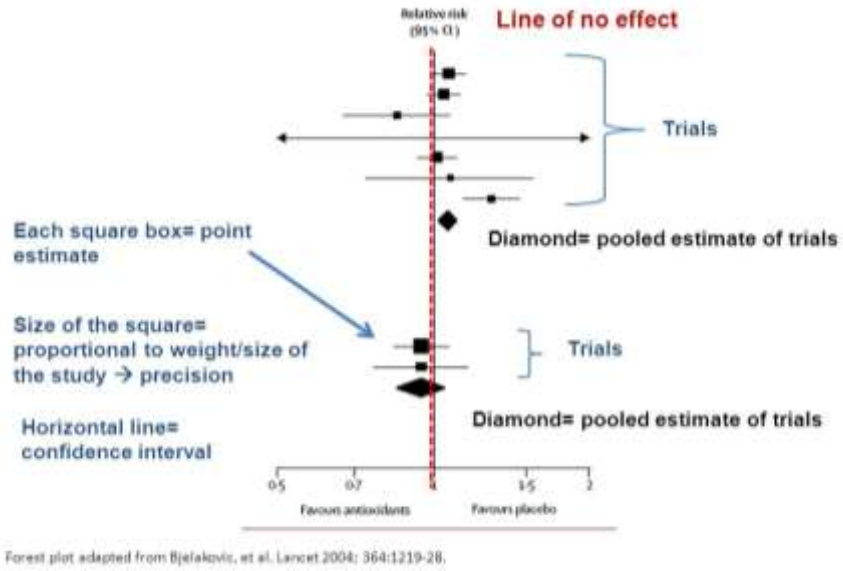

Figure 1: Reading a Model Forest Plot [36]

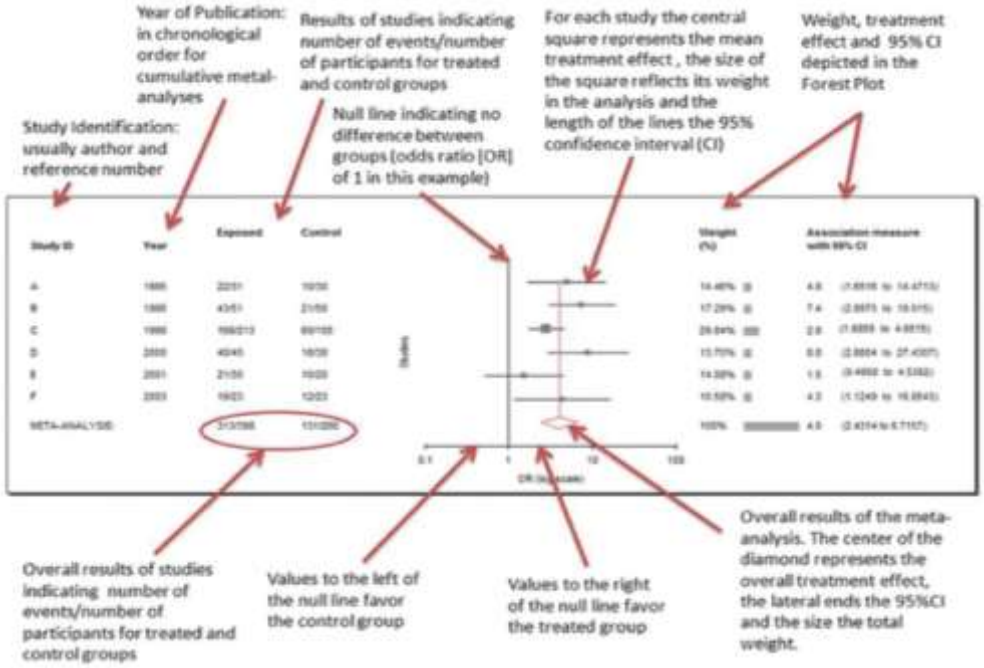

Figure 2: Reading a Model Forest Plot [37]

Effect sizes are stated along with a 95% confidence interval (CI) range, and presented in both quantitative format & graphical representation as forest plots (Model Forest Plot - Figure 1 & 2). They visually depict each trial as horizontal lines with a middle square shape, representing the extent of the CI and the effect size respectively. The graph is presented with a centre line representing the 0 mark (Line of No Difference). Often the left side of the graph (> 0) favors the treatment, while the right side (< 0) favors the control condition. At the bottom of the graph is a summary effect size (Diamond Shape) representing the pooled results of all individual studies together.[4,38]

IV. CONCLUSION

A meta-analysis is a statistical method used to estimate an average, or common effect, over several studies, usually based on the results of Randomized controlled trials. Meta-analysis can be performed when there are multiple scientific studies addressing the same question and each of the individual study reporting measurements that are expected to have some degree of error. These errors are statistically averaged out giving a 'Pooled Effect estimate'. Also the test for heterogeneity of the effect on outcome between the included studies examines the null hypothesis that all studies are evaluating the same effect. Graphically represented Forest Plot gives an easy understanding of the Effect of individual Studies and Pooled Effect of all studies. Though executing a Meta-analysis is an exhaustive task, the importance of its applications cannot be ignored. In fact the highest level of Evidences obtained by Meta-analysis is needed for deciding Clinical Practice Guidelines & Informed Clinical Decision makings and drafting the Public Health Policy Guidelines by Government agencies.

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