CME

Understanding of Study Designs in Clinical Research: Major Prompting Points

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Study design plays an important role in clinical epidemiology and public health. This helps in not only quantifying the level of relationship between exposure and outcome accurately but also in differentiating whether a measured relationship between an exposure and outcome is an indication of mere association or suggestive of risk/causality. It also helps in quantifying the prevailing burden of disease/disease frequency (i.e., prevalence, incidence rate, incidence density rate) in a considered region. Study designs are classified mainly based on evidence regarding the involvement of the comparison group; control of exposure (e.g., treatments) in the hand of the researcher (yes/no); exposure precedes outcome (e.g., cure) or not; use of randomization (yes/no); timing of data collection (i.e., before occurrence of exposure and outcome; or otherwise); and direction of data collection between exposure and outcome. Taking into account these considerations, the focus of the present write-up is to briefly describe various study designs and related merits and demerits so that researchers can be aware and make use of them to specify study designs of their planned clinical studies accurately.

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Introduction

To begin with, studies/research may be broadly categorized as quantitative studies/research dealing with numbers and statistics and qualitative studies/research dealing with mainly words and meanings. The present write up has a focus on only quantitative studies/research. Study designs[1-7] play a pivotal role in identifying various types of evidence along with their varying levels of utilities in public health management and/or clinical practice. They help in quantifying prevailing disease frequency (i.e., prevalence, incidence rate, incidence density rate) in a considered region. Also, they help in not only quantifying the level of relationship between exposure and outcome accurately but also in differentiating whether a measured relationship between an exposure and outcome is an indication of mere association or suggestive of risk/causality. Various components like involvement of comparison group (yes/no); control of exposure (e.g., treatments) in the hand of the researcher (yes/no); exposure precedes outcome (e.g., cure) or not; use of randomization (yes/no); timing of data collection (i.e., before occurrence of exposure and outcome, or otherwise); and direction of data collection between exposure and outcome (i.e., from exposure to outcome; or from outcome to exposure) help in identifying various study designs.[1-7] Accordingly, the appropriate understanding by the researchers about various study designs, and related merits and demerits may be necessary to derive reliable evidence through their clinical studies.

Study Designs

The types of studies (i.e., study designs) under clinical research may be of various types. Major designs are briefly described as follows:

Observational Study

A study where an investigator does not control/allocate exposure (e.g., smoking) among study participants is known as an observational study. All such studies may further be broadly categorized as:

I.A. Descriptive Study

An observational study[1] without involving a comparison group is known as a descriptive study. A descriptive study may generally be a cross-sectional survey.

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Accordingly, a single group cross-sectional survey is not aimed to measure any association; it is simply used to describe the profile of a study population regardless of a community or a hospital. In other words, such studies may provide prevailing distributions of various phenomena/characteristics, including the prevalence of a disease. As such, data on exposure (e.g., smoking) and outcome [e.g., coronary heart disease (CHD)], along with all other variables, are recorded as prevailing on the day of data collection. As such, there is no information on the directionality between exposure and outcome. It may be depicted as in Figure 1.

A cross-sectional survey may often provide quality data, remain inexpensive and conclude rapidly. However, it remains disadvantageous in terms of providing only simple differentials. Sometimes qualitative studies (to be communicated separately) are also referred to as descriptive studies.

B. Analytical Study

All the observational studies involving a comparative group are known as analytical studies. They are further categorized as follows:

Cross-sectional Study

A cross-sectional study is a comparative study that consists of a cross-sectional survey (as depicted in Figure 1) in two or more groups. As mentioned earlier, under this study, the data on exposure variable (E) and outcome variable (O), along with other variables (i.e., probable confounders and effect modifiers), are collected as existing/prevailing on the day of data collection. In other words, as a major limitation of this study design, no information is collected on the directionality between exposure and outcome. This study may comparatively provide quality data, remain inexpensive and be concluded rapidly. However, it may not provide an estimate of the risk ratio (to be communicated separately) and efficient sampling of rare exposure. However, this study design is used most frequently, more so related to dissertations/thesis of PG students enrolled for MD/MS/DM/MCh/Ph.D. degrees. As a matter of fact, such studies may simply provide an association between exposure and outcome which might help in a better way to decide research questions/hypotheses/objectives for future studies involving better study designs. As obvious, diagnostic studies (to be communicated separately)[8] also fall under cross-sectional studies.

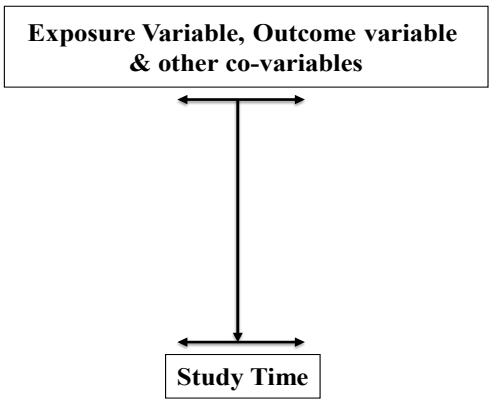

Figure 1: Cross sectional study

Cohort Study

A cohort study is basically a comparative study between an exposed group (e.g., smokers; toxic gas exposed) and non-exposed group (e.g., non-smokers; non-toxic-exposed) with a focus on timing of the study as well as directionality of data collection on exposure and outcome (e.g., coronary heart disease (CHD)). Accordingly, it may further be categorized as:

Retrospective Cohort Study

A cohort study started after the onset of exposure and outcome is called a retrospective cohort study. It may further be categorized into two groups in view of the directionality of data collection on exposure and outcome.

Forward Retrospective Study

A retrospective cohort study is called a forward retrospective study if data is collected first on exposure and then on the outcome. It is also called a historical cohort study (Figure 2). For instance, regarding the gas disaster on the night of 2nd/3rd December 1984 in Bhopal, Madhya Pradesh, this study design was used to collect detailed information on toxic gas exposure and acute phase morbidities.[9] Some publications using acute phase data may be referred to in the supplementary volume of the Indian Journal of Medical Research and also in a technical report on population-based long-term epidemiological studies of the then Bhopal Gas Disaster Research Centre (presently as National Institute for Research in Environmental Health, (Indian Council of Medical Research), Bhopal).[9-11]

Backward Retrospective Study

Contrary to a forward retrospective cohort study, under a backward retrospective cohort study, data is collected/observed first on outcome and then on exposure. It is also called a case-control study[2] (Figure 3). For instance, regarding the gas disaster on the night of 2nd/3rd December

1984 in Bhopal, Madhya Pradesh, this study design could be used for analysis through consideration of all deaths among registered cohort (exposed and unexposed) after due time and randomly (to be communicated separately) selected representative and required number of healthy controls from registered cohort (exposed and un-exposed both). Under a case-control study, one may consider varying the number of controls per case depending on the feasibility and objectives of the study. For instance, if the objective is only to assess possible determinants along with exposure, one-to-one consideration may serve the purpose. But, if the purpose is to prioritize among the determinants, consideration of multiple controls per case may be required.

Prospective Cohort Study

As an observational study, a prospective cohort study consists of a long-term follow-up of a group of people with their known/observed status regarding a particular exposure (yes/no) with a focus on assessing its possible association with an outcome of our interest among them. In other words, as an observational study, a prospective cohort study is started before onset of the main outcome. It may further be categorized into two groups in view of the directionality of data collection/observation on exposure and outcome.

Forward Prospective Study

A prospective cohort study is called a forward prospective study if data is collected/observed first on exposure and then on the outcome. It is also called a prospective cohort study (Figure 4). For instance, regarding the gas disaster on the night of 2nd/3rd December 1984 in Bhopal, Madhya Pradesh, this study design has been used to follow some of the known toxic gas-exposed and non-exposed people at specific intervals to record symptomatic morbidities along with chronic morbidities like COPD, CHD; and also mortality among them[10-11]. Some related analytical results may be available in related technical reports of the then Bhopal Gas Disaster Research Centre (presently, National Institute for Research in Environmental Health)[10-11]. As such, prospective cohort studies often remain longitudinal and involve more time and cost. For example, long-term epidemiological studies, as well as a population-based cancer registry in Bhopal established after toxic gas exposure, are still continuing.

Backward Prospective Study:

Contrary to a forward prospective cohort study, under a backward prospective cohort study, data is collected/considered first on the outcome and then on exposure. It is also called as a nested case-control study (Figure 5). For instance, regarding the gas disaster on the night of 2nd/3rd December 1984 in Bhopal, Madhya Pradesh, this study design could be used for analysis through consideration of all patients suffering from one of the chronic diseases like newly identified chronic obstructive pulmonary disease (COPD) among registered cohort (exposed and unexposed) after due time and randomly selected representative and required number of controls from the same cohort. As a basic difference between this design (i.e., a nested case-control study) and earlier described backward retrospective design (i.e., case-control design), outcomes are recorded prospectively under this design whereas retrospectively under backward retrospective design. Otherwise, all considerations under this design are similar to those under backward retrospective design. As obvious, comparatively, the data under this design does not involve much recall bias.

Experimental Study

A study where an investigator controls/allocates exposure/intervention (e.g., yoga; drug) among study

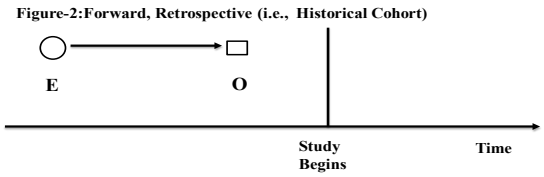

Figure 2: Forward, Retrospective (i.e., Historical Cohort)

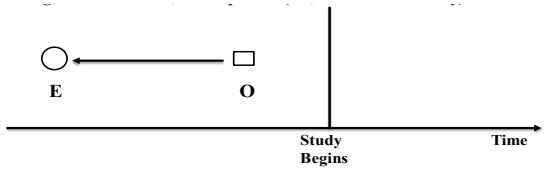

Figure 2: Backward, Retrospective (i.e., Case Control Study)

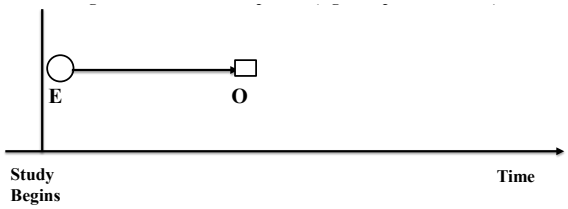

Figure 4: Forward, Prospective (i.e., Prospective Cohort)

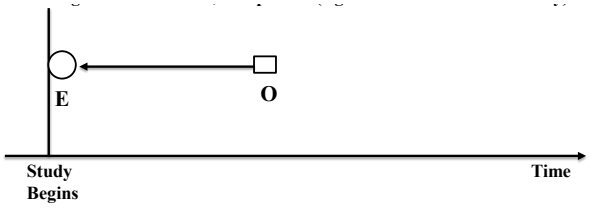

Figure 5: Backward, Prospective (i.e., Nested Case Control Study)

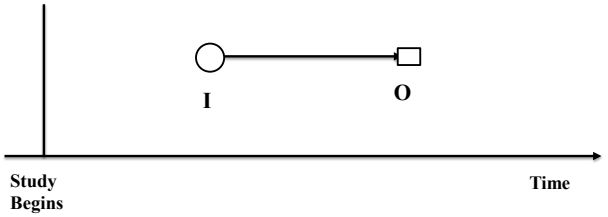

Figure 6: Forward, Prospective (i.e., Non-Randomized Controlled Trial)

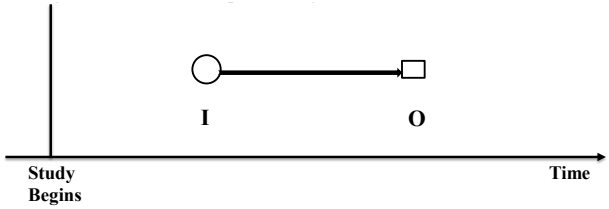

Figure 7: Forward, Prospective [i.e., Randomized Controlled Trial (RCT)]

participants is known as an experimental study.[4-7] Under frequent use of parallel design, in the case of two drugs, one intends to compare either a new drug with a placebo (i.e., no-drug) or a new drug with a standard drug that is already in use. Although rarely used, in the case of cross-over design, each patient receives both drugs in a selected sequence randomly, the first drug followed by the second drug, or the second drug followed by the first drug. For conceptual understanding further, focusing on parallel design, all such studies may further be broadly categorized as:

Non-Randomized Controlled Trial:

Under this design (Figure 6), in contrast to analytical observational studies, specific intervention (I) is allocated to the study participants by the investigator without involving random allocation (to be communicated separately). In other words, a drug to be given to a patient is decided solely by the treating clinician under routine clinical practice, and then experienced outcomes (O) are recorded after completion of the pre-decided treatment period in each arm of the study. Therefore, due to the non-random allocation of the considered drugs to the considered patients, findings under such studies may not provide reliable comparative efficacy of the new drug. To be more specific, evidence derived from such studies may not be valid to guide related clinical practice. Sometimes, such studies are also referred to as quasi-experimental studies or semi-experimental studies.

Randomized Controlled Trial (RCT)

Under this design (Figure 7), in contrast to a non-randomized controlled trial, specific intervention (I) is allocated to the study participants by the investigator with due consideration of the unpredictable random allocation method (to be communicated separately). In other words, a drug to be given to a patient is neither decided by the treating clinicians nor do they know about the specific arm of a patient. In other words, both components of randomization (unpredictable random allocation sequence and concealment) need to be maintained by a third person who is not part of the research team. The experienced outcomes (O) by the patients are recorded after completion of the pre-decided treatment period in each arm of the study. The RCTs may broadly be of two types.[4,6]

Randomized Open Clinical Trial (Open RCT)

The RCTs in which everyone involved in the trial knows about treatment groups and which group is receiving which intervention are called as open RCTs. This sometimes raises pertinent questions related to expected bias in recorded data especially on outcomes.

Randomized Blind Clinical Trial (Blind RCT)

The RCTs in which everyone involved in the trial does not know about treatment groups, groups receiving specific interventions, are called blind RCTs. They may further be sub-categorized as single-blind RCT, only the study participants or investigators recording outcomes are blinded; double-blind RCT, both the study participants and investigators recording outcomes are blinded; and triple-blind RCT, all the study participants, investigators recording outcomes, and data analyst are blinded. If and when feasible, to overcome the problem of expected bias, blind RCTs need to be preferred.

Due to the random allocation of the considered patients to the considered drugs, regardless of open and blind RCTs, findings under such studies may often provide reliable comparative efficacy of the new drug. To be more specific, findings derived from conclusive RCTs may often emerge as be best evidence to guide related clinical practice. Due to the strength of evidence derived through such a valuable study design, there has been continuing emphasis on evidence-based health care in general and evidence-based medicine in particular.

Phases of Clinical Trials

To begin with, as an attempt to identify novel interventions/drugs, including their mechanism of action and probable specific effects, necessary basic research has to be carried out as an in vitro study followed by animal studies in the form of discovery research. Once successful, as an attempt to develop interventions regarding prevention, screening,

diagnosis, and management of a health issue/disease along with related side effects, related randomized controlled trials have to be carried out in various phases through the execution of well-written protocols covering varying objectives:

Phase-0 Trial

Although not always mandatory, as a first study on human beings, it is often conducted in healthy volunteers to observe the metabolism of the body with the considered drug. If this drug shows the expected biological results among humans, then only the next phase of the study may be carried out.

Phase-I Trial

Often, as a first study in human beings to assess safety, identify adverse effects, and range of safe doses, this study involving a small number of healthy volunteers is conducted. Trial size under this phase is conventionally decided in view of the primary concern with the safety of study participants. In other words, as a rule of thumb, a total of 10 to 30 participants should be sufficient to reveal meaningful differences in the considered outcome.

Phase-II Trial

After successful completion of the phase-I trial on the considered drug along with convincing expected observations, as an explanatory RCT, a phase-II trial involving a large number of related patients (not involving many co-morbidities) is carried out with a major focus on assessing its efficacy, and also study safety, side-effects, and safe doses. As a rule of thumb, 100 to 200 patients may be included in each arm of the study. Although not mandatory, it is better to allocate patients using the appropriate randomization method (to be communicated separately). Further, because of feasibility issues, even a phase-II trial is often carried out on a smaller number of patients in each arm (i.e., a pilot Phase-II trial). Regardless of number of considered patients under the phase-II trial, findings remain suggestive, not conclusive.

Phase-III Trial

As an explanatory RCT, It is virtually a conclusive study to provide reliable evidence for public health/clinical practice. Hence, this phase of the trial is carried out under strict conditions (including consideration of minimum sample size and randomization regarding allocation) mainly to compare it with a standard drug or placebo, confirm its efficacy, and monitor related side effects. For deciding the minimum required sample size to answer the planned research question (s), results under the phase-II trial are considered. If necessary, to cover the required minimum sample size, a multi-center study may be explored under the supervision of a central coordinating center to complete the study within a stipulated time. Further, this study also involves the most appropriate use of the randomization method to allocate patients to various treatment arms of the study. As such, if there is no phase-II trial on considered drug/intervention, a phase-III trial may not be planned. In such a situation, to begin with, a phase-II trial needs to be carried out. In summary, to keep the phase-III trial conclusive, consideration of the minimum sample size required for the study and the use of appropriate randomization methods are a must.

Phase-IV Trial

A drug/intervention may be considered for its approval regarding its use in public health/clinical practice only after the successful completion of a conclusive phase-III trial described above. Once approved by the central drug authority (Drug Controller General of India (DCGI)), the drug/intervention may be available for its day-to-day use in public health/clinical practice among the general population, which is conventionally referred to as a phase-IV trial. The monitoring under this phase is primarily related to assessing the effectiveness of the drug in the general population and also its safety (i.e., long term effects). As such, this phase of trial is known as pragmatic RCT.

Types of Phase-II/III RCTs involving Varying hypothesis

The randomized controlled trials (RCTs), especially Phase II and Phase III, may further be categorized in view of their considered hypotheses, which differ in methodology and reporting[6,7]:

Superiority Trials

This trial is used mainly when there is no standard intervention/treatment available for a disease. In other words, a newly considered intervention/treatment is being assessed regarding its efficacy in comparison to a placebo. Accordingly, the hypothesis of such studies may be specified as "either of newly proposed treatment and placebo" and may be superior to each other. Likewise, this trial may also be used if researchers are not sure about the comparative superiority of two interventions/treatments proposed/available for the same disease. In this case, the hypothesis of studies may be specified as "either of the two available/proposed treatments", may be superior to each other. Above hypotheses may also be

expressed as average improvement under new treatment may not be comparable with average improvement under placebo; and average improvement under first treatment may not be comparable with average improvement under second treatment respectively.

Non-inferiority Trials

This trial is often used to assess the non-inferiority of a newly proposed intervention and/or dose of a drug in comparison to available standard intervention and/or dose of a drug regarding treatment for a disease, considering a well-defined threshold of difference in experienced outcome as non-inferiority. Accordingly, the hypothesis of such studies may be specified as, "Newly proposed dose/intervention may be non-inferior to existing dose/intervention, to achieve a pre-planned outcome within a pre-specified threshold of non-inferiority." For example[12], keeping in view of lesser side effects and no need for isolation rooms for admission, a lower radioactive iodine dose for treatment of thyroid cancer patients may be considered non-inferior to achieve ablation after six months of the first dose in comparison to its higher dose even if lower dose helps in achieving ablation among a lesser number of patients (i.e., comparative difference up to 15%). In other words, at considered optimum difference (e.g., comparative difference up to 15%) in the experienced outcome as a non-inferiority threshold, a newly considered low dose of an existing drug may be assessed regarding its non-inferior efficacy in comparison to an existing higher dose of the same drug. In a broader perspective, the above hypotheses may also be expressed as average improvement under new dose/treatment may be non-inferior to average improvement under existing dose/treatment at considered optimum difference (e.g., comparative difference up to 15%) in experienced outcome. It may be worthwhile to mention here that the non-inferiority margin has to be decided through thorough discussion with the related clinicians. Sometimes, due to ignorance, this trial is sometimes addressed as an equivalence trial (defined later)[12].

Non-superiority Trials

The use of this trial is almost negligible. For completeness of understanding**,** in contrary to non-inferiority trial, this trial may be used to assess the non-superiority of a standard intervention and/or dose of a drug in comparison to newly proposed intervention and/or dose of a drug regarding treatment for a disease, considering a well-defined threshold of difference in experienced outcome as non-superiority. For example, while treating thyroid cancer patients, a higher radioiodine active dose may be considered non-superior to achieve ablation after six months of the first dose in comparison to a lower dose if a lower dose is able to help in achieving ablation among a higher number of patients (e.g., comparative difference as 15% or more). Accordingly, hypotheses of such study may be expressed as average improvement under standard dose/treatment may be non-superior to average improvement under newly proposed dose/treatment at considered optimum difference in experienced outcome (e.g., comparative difference as 15% or more).

Equivalence Trials

This trial is nothing but a pooling of non-inferiority and non-superiority trials together[7]. To be more specific, this trial may be used to assess the indistinguishability of standard intervention and/or higher dose of a drug and newly proposed intervention and/or lower dose of the same drug regarding treatment for a disease, considering a well-defined range of difference in experienced outcome between two treatments as indistinguishable. For example, while treating thyroid cancer patients, a higher radioiodine active dose may produce either a higher ablation rate after six months of the first dose in comparison to that with its lower dose; or vice versa. Both doses may be considered equivalent If the comparative difference is in a pre-specified range (e.g., -15–+15%). Accordingly, hypotheses of such study may be expressed as the average difference in ablation rates under standard dose/treatment and newly proposed dose/treatment may be indistinguishable/equivalent at a pre-specified level (e.g., the comparative difference may be in a range of -15–+15%).

Systematic Review and/or Meta-Analysis

To ensure evidence based health care, one requires adopting a conscientious, explicit, and judicious use of current best evidence in making decisions about the care of individual patients. For this, there is a need of a systematic review of the evidence on a clearly formulated question using systematic and explicit methods to identify, select, critically appraise and synthesize the studies. A statistical technique (i.e., Meta-analysis) is used to synthesize the effect size of considered outcome (s) from various eligible studies.

The systematic review with or without meta-analysis, is useful if there are conflicting findings under multiple studies considering the same research question and study design, especially in the case of randomized controlled trials. Similar to all study designs briefly described

above, the process under systematic review of various available studies also starts with a written protocol including descriptions of a specific research question(s), intervention/outcome, inclusion and exclusion criteria for the studies, searching the studies in literature, data collection for the studies, quality assessment of the studies and carrying out a critical analysis of the observed findings under the studies. However, to combine the collected data under systematic review, meta-analysis (consisting of statistical methods) is involved only if there is two or more studies (especially RCTs) considering the same outcome.[13-15] In other words, every systematic review may not involve meta-analysis. Meta-analysis is likely to provide a more precise measure of the efficacy of intervention than that under individual study.

For example, among the total RCTs available on assessing the efficacy of neo-adjuvant chemotherapy regarding breast-conserving surgery (BCS) among breast cancer patients in comparison to adjuvant

Chemotherapy, some of the RCTs might have revealed efficacious results related to a specific outcome where as remaining otherwise. In such a situation, a systematic

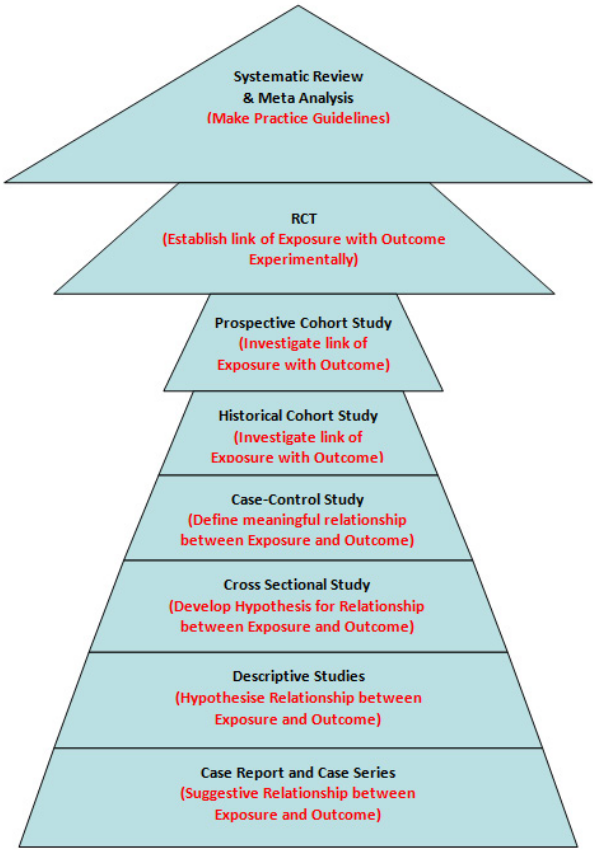

Figure 8: Hierarchy of evidence regarding relationship between exposure and outcome

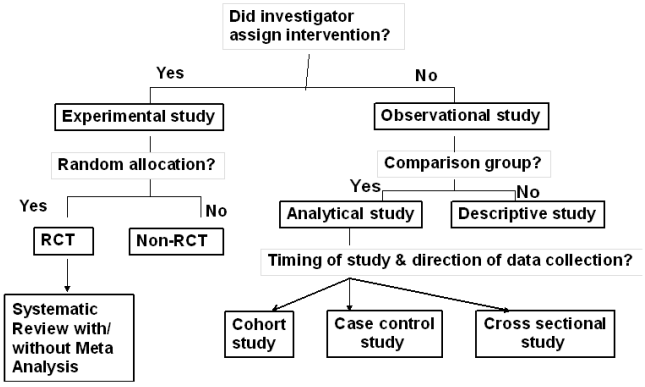

Figure 9: Study designs

review with or without Meta-analysis is used[13-15]. As stated earlier, involvement in meta-analysis is appropriate only if there are two or more RCTs considering the same outcomes (e.g., BCS). As evident from the depicted hierarchy (Figure 8), in such a situation, the quality of evidence regarding the relationship between intervention/exposure and outcome remains stronger in the case of a related systematic review and Meta-analysis.

When there is involvement in comparing two treatments of a disease with a specific outcome, the above-described pairwise Meta-analysis may serve the purpose, but sometimes, there might be multiple treatments available for a disease. As such, under such a situation, there might be studies comparing different types of treatments. Hence, there may be a need to strengthen the derived evidence using pairwise meta-analysis of very few RCTs. Further, there may also be a desire to assess two treatments that are not compared directly in any randomized controlled trial but have been compared with common comparators. To achieve such objectives under a systematic review, an indirect technique, "network meta-analysis," may be used[16-17]. This analysis also facilitates to ranking of the multiple treatments in order of preference, which is not possible based on merely efficacy under pairwise meta-analysis.

Conclusion

Any research proposal invariably involves a mention of study design in view of the research question of a study. A clinical researcher may easily conceptualize and briefly describe various study designs earlier and include an accurate design of his study in the concerned written protocol/proposal of the study. Nowadays, even a properly written protocol (especially of RCT/systematic review and Meta-analysis) may also be published.[16] The study designs described above may be summarized as depicted

in Figure 9. The studies may be either observational or experimental in view of control of the investigator on intervention. To be more specific, there is control of the researcher on intervention under experimental studies there is no control on intervention (i.e., exposure) under observational studies. Observational studies may also be broadly categorized as analytical studies involving comparative groups or descriptive studies without involving a comparative group. Further, analytical studies may broadly be categorized as cross-sectional study, case-control studies, and cohort studies in view of the timing of the study and the directionality of data collection between exposure and outcome. If there is an absence of directionality between them, such studies are simply known as comparative cross-sectional studies. If disease occurs after exposure but data collection on disease status precedes that on exposure status retrospectively, such studies are classified as case-control studies. One needs to differentiate between comparative cross-sectional study and case-control study correctly. Contrary to case-control studies, if data collection on exposure status precedes to that on disease status prospectively, such studies are classified as prospective cohort studies. A prospective cohort study may be further classified as an experimental study if exposure (i.e., intervention) is under the control of the researcher. As such, an experimental study becomes a randomized controlled trial (RCT) if study participants are randomly allocated to considered interventions. As obvious, the evidence obtained under a full phase-III trial only serves the purpose of guiding public health/clinical practice. As a matter of fact, a pilot/preliminary phase-III trial does not allow concluding the findings; it remains a suggestive/indicative finding.

In the case of a number of studies on the same topic, especially RCTs, if there are conflicting findings on the efficacy of an intervention, an appropriate pairwise Meta-analysis has to be carried out to derive the current best evidence in making decisions about the care of individual patients. Further, in case of availability of multiple treatments for a disease, one can carry out systematic review and network Meta-analysis to derive not only more precise results using a small number of available trials but also obtain comparative results related to two treatments that are not compared under any RCT directly but individually assessed with a common comparator. In addition, to answer obvious queries, multiple treatments may be ranked in order of preference, which is not possible through pairwise Meta-analysis.

It may be worthwhile to mention here that planning, execution, data collection, management, analysis, and interpretation are guided by not only the research question but also by used study design. To ensure this, there are specific guidelines for reporting results under a study using a specific study design.[17-20] It is advisable to go through concerned study design-specific guidelines while preparing a study protocol so that it helps in clarifying various aspects involved in the study.

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