CME

What are the Major Research Methodology Steps under a Clinical Study?

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Keeping in view of the need for quality evidence for public health care/clinical practice, along with focus on adopting a culture of strong morality at every level of a research work, it is necessary to follow each of the major steps required under research methodology for a clinical study. Accordingly, the present write-up aims to briefly list major steps under research methodology so that a reader can easily be aware of them at a glance and choose and follow all relevant/applicable steps in their clinical study. If feasible, except two steps (sample size & scales of measurements) which are already published in earlier issues of this journal, each of the remaining major steps may be elaborated separately and published in the ensuing issues of the journal.

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Introduction

Clinical research is majorly carried out to derive an authentic and reliable evidence to guide public health and/or clinical practice. As a first step in this direction, to strengthen the study, including derived findings/inferences, the researcher of a particular study is supposed to prepare a study protocol after being fully aware and well acquainted with major steps under the required research methodology.[1] Nowadays, a well-written protocol for clinical studies like randomized controlled trial/systematic review & meta-analysis get published in reputed journals. A researcher may or may not be in position to follow each of these steps under research methodology of a particular study, but he needs to be familiar so that in case of any deviation at any of the required steps, he understands related limitations of the study and its implications while interpreting the analytical results and deriving conclusions including generalizations of the results. The present write-up aims to briefly address all the major steps under research methodology regarding a clinical research. If feasible, each of them may be elaborated as individual CMEs in this journal itself which may obviously be helpful to strengthen quality clinical research.

Review of Literature

To begin with, an extensive/exhaustive systematic review of literature in the area of concerned specialty is must to know about various topics, related available documents, reported priorities and lacunae in existing literature. Through a critical appraisal of the existing literature, the knowledge about gaps is crucial not only to identify a specific research question for a clinical study but also it's rational in detail. Sometimes such review may provide a number of research questions to be addressed through a couple of studies. Also, a comprehensive systematic review of literature can easily be presented in an article form for its possible publication.

Research Methodology

As a matter of fact, research methodology consists of two components; one is research, and another is related methodology. On the one hand, research literally refers to a systematic investigation to answer a specific research question. On the other hand, methodology under specific research refers to the required systematic methods involved at various steps under a clinical study. The major steps, listed below and described briefly, need to be clearly stated in the protocol of each and every study. It may be worthwhile to mention that planning some of

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the clinical studies involves much more time to avoid ambiguity and ensure clarity. It may facilitate in following every step documented in protocol more objectively while doing the study.[1] As such, good practice is the need of the hour, more so if clinical studies, including randomized controlled trials (RCT), are planned to be carried out. There should be no place for manipulation to ensure quality research. There will be no exaggeration to say that morality stands above research methodology. As prompting points, the major steps under research methodology are briefly described in successive sections with a special focus on quantitative clinical studies. This may also help equally in understanding the required steps under research methodology in relation to other types of studies.

Step 01: Research Question/Hypothesis/Objective of the Study

To carry out any clinical study, one needs to be very clear about the specific research question(s) being addressed under the study. Its research framework should follow the criteria of FINER (feasible, interesting, novel, ethical, and relevant). It might be broadly of two types: estimation and/or testing of hypothesis. For instance: What proportion of patients attending a pulmonary medicine OPD in RD Gardi Medical College, Ujjain, is found suffering from respiratory problems? Whether a newly developed drug to treat respiratory patients is efficacious? A study may involve one or more than one research question. They may be basically primary or secondary research questions. As obvious, the planning of a study is mainly guided by a major focus on its primary research question and associated hypothesis/objective. Hence, a study may preferably address one primary research question.

Through the adoption of elements of PICO (population, intervention, comparator, and outcome), a specific research question leads to a hypothesis of the study, which further leads to the objective of the study:

Research Question → Hypothesis → Objective

For example: In case of pulmonary disease in a population:

Research Question: Is a newly developed drug efficacious for treating pulmonary disease?

Hypothesis: A newly developed drug may be efficacious for treating pulmonary disease.

Objective: To study the efficacy of a newly developed drug to treat pulmonary disease.

To clarify further, the hypothesis of a study is nothing but an alternative hypothesis under the testing of the hypothesis. Depending on the alternative hypothesis, it may be either one-sided or two-sided. It should not be written in the form of null hypothesis. As stated earlier, it may be better to address one major primary objective under a study to make it more meaningful. However, if any more, other objectives may be listed as secondary objectives.

Step 2: Study population

It may be worthwhile to document the target study population and related characteristics clearly. For example, if RCT has to be carried out among breast cancer patients (stage I to stage IV), all patients, regardless of stages, will be part of the target study population. In other words, findings under a particular RCT on a representative sample of such patients may be generalized among the target study population. Likewise, if the prevalence of respiratory disease among patients visiting respiratory clinics is required, all the patients visiting such clinics will constitute related study population.

Step 3: Intervention/Exposure under the study

An exposure variable may be either a protective factor (e.g., physical activity) or a risk factor (e.g., smoking) while dealing with coronary heart disease (CHD) under an epidemiological study. Like need of optimal scale of exposure variable (e.g., smoking), under a clinical study involving an intervention (e.g., drugs), intervention needs to be spelled out clearly in terms of dose/frequency/timings and duration in view of the clinical rationale and/or available quality evidence in this regard. As pointed out earlier,[2] ambiguity in scale of measurement of even a single covariate, including exposure/intervention variable, has potential to distort the results under a clinical study.

Step 4: Comparator

To assess the association of smoking with CHD under an epidemiological study, along with smokers, and non-smokers are also taken as comparator. Accordingly, CHD prevalence or incidence cases are compared between smokers and non-smokers. Likewise, under a RCT, along with newly proposed intervention/drug arm, there has to be a comparator group in form of a placebo or a standard intervention/drug arm. This needs to be specified in a lucid and clear manner.

Step 5: Outcome (s) under the study

On the lines of exposure variable, an outcome may also be either a best/better outcome (e.g., cured/improved) or a worst/bad outcome (e.g., death, deterioration). A specific

outcome (e.g., cured/improvement in biological markers/death) must be specified for comparison in relation to an intervention/non-intervention, and its recording criteria (including timing after initiation of intervention) must be documented clearly. If feasible, understudies like randomized controlled trials, person recording outcomes is blinded about received interventions by the participants in different study arms. Such a good practice ensures accuracy in outcome recording, more so in case of multiple persons involved in this regard. Otherwise, final results/inferences under the study get influenced due to under/over estimation of outcomes.

Step 6: Disease under the study

As discussed regarding exposure/intervention under the study, most updated diagnostic criteria for the disease under consideration must also be written lucid and clear. It can obviously help more in case of independent involvement of many people in diagnosis. Likewise, if healthy controls are to be included as a comparator, the related criteria should also be written clearly. Any ambiguity/misunderstanding in this regard might influence the representativeness of targeted participants under the study which can further lead to distortion in the results and derived inferences.

Step 7: Type of Study Designs

The researchers need to specify one of the various study designs in view of their research questions/objectives. There are a number of study designs under observational studies[3-7] (e.g., historical cohort studies, case-control studies, prospective cohort studies, nested case-control studies, cross-sectional studies, descriptive studies); and also under experimental studies[8](e.g., randomized controlled trials like superiority trials, non-inferiority trials, non-superiority trials and equivalence trials). Sometimes people may like to explore through crossover designs; and semi-experimental studies. Accordingly, one has to be familiar with design-specific planning, execution, type of data, analysis, interpretation and possible implications.

Step 8: Sample Size

A complete enumeration of a study population may not be feasible for conducting a research study. It is always a representative sample on which a study is carried out and findings are often generalized among study population and/or other populations with similar characteristics. As pointed out earlier,[9] a minimum sample size has to be considered to obtain an appropriate answer to a research question. For this, acceptable conventional approaches/computational methods to decide a required minimum sample size have been briefly enumerated there. For a conclusive study, along with other required inputs, including level of burden/effect size, consideration of optimal level of confidence and/or power of the study is mandatory while exploring required minimum sample size. Otherwise, the study will invariably remain to be a preliminary/pilot study.[9] As obvious, exploration of minimum required sample size for comparative/experimental studies involve both components, level of confidence and power of the study; on the other hand exploration of sample size for studies aiming burden estimates involves only level of confidence.[9]

Step 9: Sampling Method

A random selection of study participants from study population, providing known chance/probability of selection for every sampling unit, must obtain a representative sample ensuring comparability of the drawn sample's characteristics with those of the study population. There are various random (i.e., probability) sampling methods[3] (e.g., simple random sampling, systematic random sampling, stratified random sampling, cluster random sampling, multi-stage sampling, and multi-phase sampling) to obtain a representative sample which strengthens the study in obtaining reliable and valid results along with its generalization. To be more specific, In this regard, one needs to prefer one of the random sampling methods as per feasibility. For instance, some of them involve use of a sampling frame, a list of sampling units, which may not be available sometimes. Often sampling has to be done at higher levels also instead of individuals, like households, village/urban-wards, blocks, districts, states; and in hospitals, like consultants, clinics/OPD, wards, departments, hospitals. In addition to random sampling methods, there are some non-random sampling methods (e.g., purposive/convenience sampling, volunteer sampling, judgment sampling, quota sampling and snowball sampling) also which may occasionally be used for an exploratory study including qualitative studies.[3]

Step 10: Random Selection/Random Allocation

Observational studies invariably involve a random selection of study participants from study population. Keeping in view of its scientific strength, while conducting a clinical study, one should use a feasible random selection method using random number table. Otherwise, like tossing a coin approach, the selection of study participants may become non-random resulting into a non-representative sample from the study population.

In multi-stage sampling,[3] one needs to retain random process at every stage like state, district, block, village/urban-ward, households and individuals. Likewise, in case of multi-phase sampling, one needs to maintain random process at every phase like registered main cohort, a random sample from registered cohort for the respiratory study, a random sample from the respiratory study group for radiological study, a random sample from the radiological study group for immunological study, and so on.

In contrary to observational studies, randomized controlled trials also involve random allocation of study participants in different study arms like drug/intervention arm; and placebo/non-intervention arm. There are various allocation methods[3,8] like simple random allocation methods, permuted block randomization, and others. One has to choose one of them appropriately in view of type and size of the trials. It may be pointed out here that haphazard allocation (e.g., patients presenting themselves alternatively in sequence, at different timings of the day, weekly, monthly and others) is not a random allocation. Further, often equal allocation of the study participants in different study arms serves the purpose, but sometimes, unequal allocation becomes necessary.[10]

Step 11: Blinding Process

Many of the clinical studies like randomized controlled trials (RCTs) get strengthened scientifically through possible involvement of blinding about arm-specific given intervention/drug. For example, blinding of only patients may be referred as a single blind trial; blinding of both, patients and investigators may be referred as double blind trial; and blinding of three patients, investigators & biostatistician may be referred as triple blind trial. The blinding helps in avoiding any bias while reporting, recording and analyzing the data on main outcomes of the study. Where ever feasible, one needs to involve blinding in clinical studies to the extent possible to generate more reliable evidence than open studies.[8]

Step 12: Data collection methods

The methods of data collection should be detailed in each aspect[1,3] like up-to-date tools/techniques (standardized/modified/newly developed) for data collection on a topic, respondent, interviewer, timings of data collection and others. The adapted methods need to be acceptable scientifically and able to produce quality data under the study. Further, if the various clinical parameters involve varying instruments/laboratories for their estimations/testings, the instruments/laboratories need to be listed against each parameter which may facilitate required monitoring. The expected eventualities also need to be identified while planning a study and their possible solutions should be spelled out. For example, to name a few, failure of an instrument, no response, and non-availability of the respondent at planned time and loss to follow-up. In the present era of digital world, data on every covariate including exposure and outcome variables need to be collected in a raw form providing the opportunity to decide appropriate modified forms of scales of measurements while understanding the data at later stage.[2]

Step 13: Data and Safety Monitoring Board (DSMB)

In anticipation of probable side effects under clinical studies like RCTs, it is mandatory to constitute a DSMB involving an independent group of experts like subject experts, trial experts, biostatisticians and others, following available guidelines in this regard.[8] The responsibilities of DSMB involve review of protocol before implementation and define the processes, including scheduled/unscheduled reviews of available data regarding safety, study conduct, scientific validity of the trial, unblinding, analysis and stopping rules. As a result of a specific review, the DSMB is empowered to decide about the continuation/discontinuation of the study with/without modifications in the protocol.

Step 14: Standard Operational Procedure

For a planned clinical study, especially RCTs, standard operational procedures for every component needs to be developed in detail. It will ensure timely and quality data collection through possible monitoring at each of the identified levels. These procedures and data collection may be monitored using a developed suitable checklist and flow diagram showing possible linkages between different levels. A best help in this regard may be drawn from check-list and flow diagram for reporting of various types of RCTs under consolidated standards of reporting trials (CONSORT) guidelines.[3] Also, a good practice of developing a standard operational procedure (SOP) for a clinical study may help identify the study's comparative strengths and weaknesses.

Step 15: Multidisciplinary Approach

A clinical study often involves multidisciplinary researchers. For example, a cohort study on stroke and dementia might involve people from neurology, biostatistics, community medicine, cardiology, neuro-psychiatry, neuro-psychology, neuro-biochemistry, neuro-radiology, dentistry, dietetics &

nutrition, hematology, gastroenterology, nuclear magnetic resonance (NMR), epidemiology, maternal & child health, and social & behavioral sciences.[11] Hence, if required, it is mandatory to follow a multidisciplinary approach to ensure appropriateness and accuracy in every aspect of a study and make the study a grand success. It may be worthwhile to point out here that there is no place for ego in a team work. In presence of ego, quality research may not be expected.

Step 16: Written Consent

A provision for written consent/assent, following specific guidelines available in this regard, needs to be included in any research study involving contacts with human beings. In absence of this, a study may not be initiated. An updated guideline in this regard is always uploaded on the website of the Indian Council of Medical Research.

Step 17: Ethical Clearance

For every single study, before start of the study, an ethical clearance has to be taken by the researcher from their Institutional Ethics Committee. Therefore this should be included in the protocol without fail. An updated guideline in this regard is always uploaded on the website of the Indian Council of Medical Research.

Step 18: Registration of the Study

Many of the clinical studies involve their due registration under related systems. For example, any type of randomized clinical trial needs to be registered online at CTRI (Clinical Trial Registry - India) portal. Similarly, a systematic review and/or Meta analysis needs to be registered with International Prospective Register of Systematic Reviews (PROSPERO). Such registration may help avoid unnecessary duplication of the same study on the topic.

Step 19: Data management

Data management is an important component of a clinical study. It requires to be detailed at planning stage. The specific movements regarding data collection on various aspects, its submission to scrutiny cell, data entry, handling of error lists and finalization of data, need to be spelled out. In other words, the responsible persons at various data collection/handling levels need to be named so that inter-level coordination becomes easier to ensure final data quality. The backup of data should invariably be maintained at specific time intervals to deal with any untoward incidence. As a good initiative, a standard operating procedure may be developed in this regard, including security and use of data.

Step 20: Data Analysis

The provision for data analysis needs to be made in view of the planned hypothesis and objectives of the study.[3] The analytical methods are guided by the types (e.g., variables & their scales of measurements) and distributions of collected data. The proposed level of significance also needs to be specified in the related protocol to consider analytical results as statistically significant. The proposed time duration for final analysis of data by a trained data-analylist (i.e., biostatistician) should be sufficient to ensure accuracy in the analysis of collected data and report preparation. Understudies like RCTs, if interim analysis is unavoidable, its frequency and timings must be specified to ensure accurate analysis may be ensured8). Further, understanding statistical significance versus clinical significance goes a long way to help in not only analyzing the data appropriately but also in interpretations and deriving related implications.

Step 21: Interpretation of Results

Once data collection is duly completed and finalized through due scrutiny/inconsistency checks, it needs to be analyzed appropriately in view of the objective(s). The obtained analytical results need to be interpreted accurately. It is often noticed that even after obtaining accurate analytical results, interpretation of results is done inappropriately mainly due to no clarity about the hypothesis of the study. To overcome such problems, as stated earlier, it is better to adapt a multidisciplinary approach. In other words, both subject expert and biostatisticians must recheck the interpretation. Further, interpretations of results need to be derived solely from obtained analytical results of collected data at the pre-planned level of significance in the protocol, not based on personal perceptions. Also, one has to take care of statistical significance versus clinical significance.

Step 22: Conclusive vs. Suggestive Study

Every clinical study may not have the strength to derive conclusive inferences from the analytical results. For example, under few steps regarding drug developments (phase I trials and phase II trials), one needs to deal with only suggestive inferences instead of conclusive inferences. But, involving sufficient confidence and power in the study, a well-planned and optimally completed phase III randomized controlled trial may allow conclusions following approved guidelines. A similar approach is true in case of observational clinical studies. A new drug found clinically efficacious under phase III trial only goes in the market to be used by the

practicing doctors in hospitals/clinics (phase IV trial).[8] Conventionally, a drug reported to be efficacious under a phase III trial done outside a country may not be approved often until a bridge study in that country supports it.

Step 23: Report (s) & Article(s) Preparation

Once a research study is completed, its report needs to be prepared, finalized and submitted at the earliest convenience. There is need to document every step followed under the study and related deviation if any. There is no point in claiming those steps that could not be followed. Further, an expedited approach needs to be adopted to prepare related research articles for publication. All attempts need to be made to ensure similarity regarding data, methods and analytical results in both (i.e., reports vis-a-vis related articles). Any ambiguity unnecessarily raises suspicion about the researchers' quality of data and honesty.

Step 24: Merits & Demerits of the Study

Keeping in view of any deviation at any step from the written protocol and from acceptable updated methodologies regarding a conclusive study, the authors need to list merits and demerits of the study in related reports/research articles. It helps derive appropriate inferences and related implications from the observed findings.

Step 25: Dissemination of the Study Findings

For completeness, it is always better to make provision for dissemination of the study findings on completion of the study. In this regard, a seminar/symposium inviting people working in similar areas may be organized. It has mainly twofold objectives- one to share study and related findings, and another to receive observations/comments on the study which might help in appropriately strengthening the study's reporting.

Step 26: Authorship in the Report/Article

Everyone who actively participated in the study and/or contributed scientifically in preparation of the report/article ought to be given due credit through inclusion as one of the authors appropriately. An objective criteria used for authorship and related order will be appreciable. In any case, giving or taking gifted authorship must be avoided. If necessary, one can follow the specific guidelines available in this regard.

Step 27: Timely publications

In time publication (s) of the findings under any completed study goes in a long way to protect scientific knowledge and help the involved scientists. For example, it helps to increase the dissemination of the observed findings, visibility and accessibility of the published article, and its citations.

Summary

The above briefly described major steps under research methodology are expected to provide prompting ideas at a glance to researchers. From this, the researchers will be reminded about various important points to address while planning a clinical research study and preparing its protocol. Therefore, as obvious, prepared clinical research protocol considering applicable steps will remain crystal and clear. Further, it will be helpful to the investigators to follow while executing and carrying out the study for its logical completion. It may not be surprising if an investigator may come across the need for more steps under research methodology while planning and conducting a clinical study. To summarize, while planning/doing a clinical study, the researchers are encouraged to understand and use the above-listed major steps under research methodology.

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