

How to Formulate a Research Question, Hypothesis and Objective for a Clinical Study?

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A research study mainly addresses a specific research question (s) which is to be primarily answered after completion of that clinical study. As such, the considered research question decides the hypothesis of the study. Ultimately, the hypothesis of a study determines the objectives of that study. Generally, a study's planning also relies on the primary research question/objective of that study. Keeping in view of the pivotal role of these facts, the present write-up aims to briefly address important issues while deciding the research question, hypothesis and objective (s) of a clinical study.

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Introduction

To support the public health/clinical decision-making, the role of the best scientific evidence is well known. To identify such evidence, quality research considering an appropriate research question needs to be carried out and/ or identified through a systematic review of literature. Research is mainly a scientific process consisting of a set of appropriate methodological tools by which we answer the considered question. It can be qualitative and/ or quantitative, which broadly differ in relation to types of research questions, flexibility in study designs, instruments for data collection, forms of collected data, and analytical objectives. Qualitative research¹⁻³ helps to understand/ describe a given problem or a topic (e.g., opinions, behaviors, social contexts) from the perspectives of the population it involves. On the other hand, quantitative research⁴ helps to quantify the burden of a problem, quantify variation and assess associated/ causal relationship(s). To facilitate easy understanding, this write-up will focus on quantitative research. Levels of quantitative research (to be detailed in a separate communication) can be interventional,

including randomized controlled trials; and/ or non-interventional (observational studies), including basic (e.g., descriptive studies) and/or analytical studies (e.g., cross-sectional studies, case-control studies, and cohort studies). Research is essential for advancing scientific knowledge and/ or developing newer technologies & treatments. It may help in verifying what others have already observed and either confirm or contradict them. Also, as an invention, it may sometimes provide newer findings not observed/ reported earlier. In the present era of evidence-based health care, as amply popularized during COVID-19, quality advance research is needed. Hence, each study should start with a specific research question that addresses what the researcher would like to answer after the completion of the study.

Required Prior Knowledge

To formulate a research question appropriately, one needs to have sufficient and accurate prior knowledge about the following in their areas of speciality:

Study Population

It refers to an aggregate group of a specific population or patients³⁻⁵ among whom study findings need to be generalized. For example, in view of focus of the study,

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a study population might be general population of Ujjain city; patients coming to outpatient departments (OPDs) of RD Gardi Medical College, Ujjain; patients attending a particular outpatient department (OPD); patients of inpatient departments of RD Gardi Medical college, Ujjain; patients of a particular inpatient department; and persons suffering from a particular disease. In brief, study population may vary from one study to another study. It needs to be spelled out clearly along with due inclusion and exclusion criteria. Inclusion criteria should be decided in view of the target study population, and easy to be followed by the researchers involved in the study. Further, exclusion criteria should be able to screen persons/ patients without any ambiguity with inclusion criteria. Also, it should help exclude subgroups of persons/ patients fulfilling inclusion criteria but having some peculiar characteristics (e.g., with co-morbidities).

Exposure Variable/Intervention Variable

An exposure variable under observational studies⁶ is one of the major independent variables/ risk factors/ explanatory variables whose relationship with considered outcome (s) is focus of the study. For example, one may wish to assess smoking as a risk factor for coronary heart disease (CHD) and/ or hypertension. Likewise, one may like to assess physical activity as a protective factor for CHD and/ or hypertension. Under another study, a researcher might plan to assess the birth-spacing effect of breastfeeding. In every case, data on an exposure variable (e.g., smoking; physical activity, breastfeeding) should be recorded in a raw form, providing an opportunity to appropriately finalize its scale of measurement through exploratory analysis. It may be worthwhile to mention that a change in scale of measurement⁷ of a single covariate in a study is expected to change the results; hence, objective consideration in this regard will go in a long way to provide accurate results. On similar lines, the considered intervention (e.g., drug; doses) under the control of the researcher in an experimental study (randomized controlled trials) serves as an exposure variable. In a clinical study, other than exposure variable, data on all other potential confounders and/ or effect modifiers (discussed separately) are used to adjust the relationship between exposure and outcome.

Outcome (s)

The considered outcomes in a study may be one or a combination of dichotomous/ multinomial outcomes, quantitative outcomes, and time to event outcomes. For example, under observational studies coronary heart disease (CHD); respiratory diseases, blood sugar; diastolic

blood pressure, and survival of CHD patients. Likewise, under intervention studies, outcomes may be death, cure, improvement, change in biological markers like diastolic blood pressure and blood sugar; and survival of chronic obstructive pulmonary disease (COPD) patients. Sometimes, a study might involve outcomes as a combination of biological markers and end-points. Each of the considered outcomes needs to be well defined to avoid ambiguity while collecting raw data on them.

Comprehensive Review of Related Literature

For a researcher as a beginner in any area of specialty, it is advisable to first carry out a comprehensive review of existing literature so that he gets familiarized with various topics covered under existing studies. Once the topic of interest is identified, he can extensively review literature, especially during recent years (e.g., last 10 years), to familiarize himself with potential research questions/hypotheses/ objectives addressed under existing studies. As a result, one can easily find out gaps in related knowledge in terms of the research question, hypothesis of the study/ objectives, definition of exposure, consideration of other variables (confounders/ effect modifiers), definition of outcomes, sample size, used instruments, methodologies and tools for data collection, types of collected data, statistical methods used in analysis and derived inferences. The knowledge about gaps in existing studies goes a long way to deciding specific research questions for the newer research topic.

Formulation of a Research Question

Basically, a research question might be conceptualized by mastering the existing literature in an area of interest, keeping the imagination at roaming, alertness about the new ideas and techniques, and continuing analysis using who, what, where, when, why, and how. To make a research question clearly expressed and easy to understand, especially for an intervention study, PICO strategy is adopted regarding the formulation of a research question where P stands for the considered study population (specific individuals/groups); I stands for the considered intervention; C stands for the considered comparator (other intervention/ no intervention); and O stands for the considered outcome. For instance, we can write: Is Neoadjuvant chemotherapy efficacious compared to adjuvant chemotherapy in treating breast cancer patients regarding functional outcome (breast-conserving surgery)?

This strategy can easily be extended regarding research question for the non-intervention study (observational studies) as well, in the form of PECO

strategy where P stands for the considered study population (specific individuals/ groups); E stands for the considered exposure (e.g. physical activity); C stands for the considered comparator (e.g., no physical activity); and O stands for the considered outcome (e.g., hypertension). Accordingly, for instance, we can write as: Is physical activity associated with hypertension among the geriatric population of a region?

The rationale for Consideration of a Specific Research Question for the Study

As a researcher in any specialization, one can easily justify consideration of a specific research question quoting the need of advancement of scientific knowledge through claim of first innovative proposal, accuracy in scales of measurements of covariates with special reference to those related to exposure/ treatment/ intervention and outcomes; newer techniques/tools; required minimum sample size; better study design; varying study population; additional important variables and measurements; appropriate statistical analysis; and limitations related to generalizations of the findings. For example, suppose there is no study available on a clinically relevant topic locally as well as globally. In that case, a study may easily be justified as a first study on the topic. Likewise, although there is study available globally, if there is no study available in India it becomes easier to justify as a first study from India. In case of the availability of studies in other regions of India, one can easily argue about the non-availability of study in the considered region along with the limitations of the existing studies on various aspects of research methodology. Even if studies are reported from the considered region, one can justify the study by pointing out pertinent limitations of existing studies on various aspects of research methodology and genuine concerns related to accuracy and valid generalizations of the findings. For instance, while conducting a study to assess the efficacy of a particular new drug/intervention/ vaccine in comparison to a standard drug/intervention/ vaccine or placebo through randomized controlled trials, simply the absence of appropriate randomization of patients in different arms of the existing studies becomes a valid justification for a new randomized controlled trial.

What Makes a Good Research Question?

A good research question has to be feasible (F). For example, the availability of adequate technical expertise, minimum required number of study subjects (patients) within the stipulated time, required time and money; and

overall management needs to be ensured. Also, this needs to be interesting (I) among the fellow researchers. Further, a research question should be novel (N), that is, ability to confirm the existing findings, to extend the existing findings; and to provide new findings. In addition, it should be approvable from an ethical (E) angle. Overall a good research question needs to be relevant (R) from points of view of scientific knowledge, health and clinical practice, and scope for future research. In summary, a good research question needs to follow a FINER criterion.

Types of Research Questions

A research question may be of broadly three types:

Understanding of a Profile

To begin with, one would like to know the profile (e.g., socio-economic and demographic characteristics along with disease status & other clinical observations) of people of specific category. For example: What is profile of patients attending outpatient departments (OPDs) in RD Gardi Medical College, Ujjain, Madhya Pradesh? What is the profile of patients attending a particular outpatient department (OPD) in RD Gardi Medical College, Ujjain, Madhya Pradesh? What is profile of patients of the inpatient department in RD Gardi Medical College, Ujjain, Madhya Pradesh? What is a profile of patients of a particular inpatient department in RD Gardi Medical College, Ujjain, Madhya Pradesh? Knowledge about such profiles generally helps in conceptualizing a future study and writing background information under various studies being conceptualized on various health issues related to such study populations.

Estimation of Burden

One may like to know the prevailing burden of specific health problems. For examples: What is burden (i.e., prevalence) of respiratory problems in Ujjain city? What proportion of patients visiting pulmonary clinics in RD Gardi Medical College, Ujjain, has respiratory problems? What proportion of patients with respiratory problems have chronic obstructive pulmonary disease (COPD)? What proportion of COPD patients treated with a particular guideline shows a pre-specified relative improvement in a marker of the patients' health-related quality of life?

Testing of Hypothesis

As another interest, one may also need to compare burden of specific health problems between two or more groups. In terms of risk measures, one may also like to assess efficacy of a particular drug/ intervention

in comparison to standard drug/ placebo regarding treatment/ prevention of a health issues. For example: Is respiratory problem burden comparable between rural and urban areas of Ujjain district? Is burden of respiratory problems comparable between patients attending medical and pulmonary clinics in RD Gardi Medical College, Ujjain? Is treatment of COPD patients using a newly proposed guidelines non-inferior to that using earlier guidelines to achieve a pre-specified improvement in a marker of the patients' health-related quality of life?

Hypothesis of the Study

The hypothesis under a clinical study is guided by its research question(s). However, as obvious, research questions listed above in first two categories do not involve hypothesis. They literally aim to obtain profile/ burden-estimates closure to those prevailing in related study population. As such, research questions listed above under third category (i.e., testing of hypothesis) provide respective hypotheses of the study as: The burden of respiratory problems may not be comparable between rural and urban areas of Ujjain district; the burden of respiratory problems may not be comparable between patients attending medical and pulmonary clinics in RD Gardi Medical College, Ujjain; and the treatment of COPD patients using a newly proposed guidelines may be non-inferior to that using earlier guidelines to achieve a pre-specified improvement in a marker of the patients' health-related quality of life. As obvious, methods regarding planning of the study and data analysis along with interpretation of the results are guided by hypothesis of the study.

It may be worthwhile to state that hypothesis under clinical study may be of four types:

Superiority Trials

In absence of any guess about comparative efficacy of involved interventions/ treatments, this trial is planned. To be more specific, if proportions of improvement/ cure rate between two arms are p_1 and p_2 , superiority hypothesis of the study may be defined as $p_1 \neq p_2$ against its null hypothesis $p_1 = p_2$. For example, the malnourished mothers treated with two different supplementations may provide varying improvement rates, first intervention showing higher or lower improvements in comparison to that under second intervention.

Non-inferiority Trials

Once it is expected that a newly proposed intervention/ drug may always provide lower improvement/ cure rate (p_1) in comparison to that under standard intervention/ drug (p_2) but with lower side-effects and/ or lesser cost, a

non-inferiority trial may be planned. To be more specific, if proportions of cure rate in two arms are p_1 and p_2 , a non-inferiority hypothesis of the study may be defined as $|p_1 - p_2| \leq \Delta$ against its null hypothesis $|p_1 - p_2| \geq \Delta$, where Δ is prespecified. For example, lower radio iodine active dose may be tested to be non-inferior to its higher dose even if it helps in achieving lower ablation rate (e.g., 13% or less) among thyroid cancer patients in comparison to that with its higher dose. Such trials are often carried out under clinical research.

Non-superiority Trials

Once it is expected that a newly proposed intervention/ drug may always provide higher improvement/ cure rate (p_1) in comparison to that under standard intervention/ drug (p_2) with similar side effects and cost, a non-superiority trial may be planned. To be more specific, if proportions of cure rate in two arms are p_1 and p_2 , a non-superiority hypothesis of the study may be defined as $|p_2 - p_1| \geq \Delta$ against its null hypothesis, $|p_2 - p_1| \leq \Delta$, where Δ is prespecified. For example, higher radio iodine active dose may be tested to be non-superior to its lower dose if it shows a prespecified lower ablation rate (e.g., 13% or more) among thyroid cancer patients in comparison to that with its lower dose. This trial is rarely carried out.

Equivalence Trials

Once equivalence of two interventions/ drugs relies on a prespecified range of difference (Δ) in effect size regardless of which of the two interventions/ drugs have higher improvements/ cure rates, equivalence trial is planned. In other words, this trial is a pooling of both, non-inferiority and non-superiority trials. To be more specific, if proportions of cure rate between two arms are p_1 and p_2 , an equivalence hypothesis of the study may be defined as $-\Delta \leq |p_1 - p_2| \leq \Delta$ against its null hypothesis $-\Delta \geq |p_1 - p_2| \geq \Delta$, where Δ is prespecified. For example, lower radio iodine active dose may be tested to be equivalent to its higher dose if there is a difference of at most 13% in ablation rates between these two arms of thyroid cancer patients. This trial is also preferred in clinical research.

Objective (s) of the Study

The objective(s) of the study is also guided by its research question (s). The objective needs to be SMART, that is, specific, measurable, achievable, relevant and time based. As such, research questions listed above in three categories provide respective objectives of the study. For examples:

Understanding of a Profile

The respective objectives may be written as: to study profile of patients attending outpatient departments (OPDs) in RD Gardi Medical college, Ujjain, Madhya Pradesh; to study profile of patients attending a particular outpatient department (OPD) in RD Gardi Medical College, Ujjain, Madhya Pradesh; to study profile of patients of inpatient department in RD Gardi Medical College, Ujjain, Madhya Pradesh; and to study profile of patients of a particular inpatient department in RD Gardi Medical college, Ujjain, Madhya Pradesh.

Estimation of Burden

The respective objectives may be written as: to study burden (i.e., prevalence) of respiratory problems in Ujjain city; to study burden of respiratory problems among patients visiting pulmonary clinics in RD Gardi Medical College, Ujjain; to study burden of chronic obstructive pulmonary disease (COPD) among patients suffering from respiratory problems at pulmonary clinics in RD Gardi Medical College, Ujjain; and to study level of pre-specified improvement in a marker of the patients' health-related quality of life among COPD patients treated with a particular guideline.

Testing of Hypothesis

The respective objectives may be written as: to compare burden of respiratory problems between rural and urban areas of Ujjain district; to compare burden of respiratory problems between patients attending medical and pulmonary clinics in RD Gardi Medical College, Ujjain; to assess efficacy of a newly proposed guidelines in comparison to earlier guidelines regarding treatment of COPD patients to achieve a pre-specified improvement in a marker of the patients' health-related quality of life through a non-inferiority randomized controlled trial.

While writing objectives of the study, it is better to differentiate between primary objective (s) and secondary objectives because planning of the study mainly relies on primary objective of the study and involved hypothesis

if any. Further, an objective might involve more than one outcomes, in such cases primary outcome needs to be specified which ultimately guides the planning of the study. For example, if primary objective involves two primary outcomes namely CHD and hypertension, as detailed in write up on sample size^{3,8}, the required minimum sample size needs to be explored for each of them and explored higher minimum sample size will be considered for the planned study.

Summary

It is worthwhile to first formulate research question (s) for any clinical study. Once research question (s) is specified, if feasible, hypothesis of the study need to be specified. Keeping in view of the identified research question and/ or hypothesis of the study, one has to specify corresponding objective (s) of the study. As such, methods regarding planning of the study and data analysis along with interpretation of the results are guided by hypothesis of the study.

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