

Clinical research methodology: A narrative review

Kalpesh Khutade *, Nisha Kumari and Harshada Shah

Department of Microbiology, Vedantaa Institute of Medical Sciences, Vedantaa Hospital and Research Centre, Palghar, Maharashtra- 401606, India.

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Abstract

Research necessitates a systematic approach, meticulous planning, and execution as planned. The study consists of predefined components, such as aims, population, conduct/technique, outcome, and statistical considerations. Understanding the fundamental aspects of methodology is crucial for any researcher, as it ensures objective, reliable, and repeatable results. This narrative review explored various aspects of the methodology used in conducting clinical research. A literature search was conducted using relevant keywords from various databases and article bibliographies.

Keywords: Blinding; Population; Randomisation; Research; Sample size; Study design; Study tools

1. Introduction

Research is the process of learning new things through careful planning, intervention, and the discovery or interpretation of new information [1]. The validity and reliability of the research should be ensured through good research, objectivity, reliability, reproducibility, appropriate practices, data collection, and explanatory reviews [2]. Relying on inappropriate or inaccurate research is unacceptable and can lead to misinformation being provided to healthcare professionals [3]. Therefore, understanding the basis of this method is important.

Aims and objectives of study

The research aims and objectives should be clearly defined and established through a thorough literature search and professional experience. The objectives and goals of a research question or problem indicate whether the problem's nature should be investigated or its solution should be found using a different method [3-6]. Existing knowledge gaps can be addressed by formulating research questions that are objectively specific, including population, intervention, control, outcome variables, and time interventions. The generation of a hypothesis, a scientifically derived statement about a specific problem in a specific population, is influenced by the type of study. Researcher observation initiates hypothesis generation, followed by a cross-sectional survey, observational study, and finally, an experiment to test the hypothesis [4-9].

2. The study flow in an experimental design

The study flow in an experimental design involved several sequential steps (Figure 1). Population refers to the group of individuals, things, or cases that are the focus of investigation and is the reference or target population for extrapolating study outcomes [4]. A researcher must determine whether it is feasible to study all individuals. For a specific outcome after identifying the target population. A study population was sampled to ensure equal and non-zero chances of inclusion for all individuals, as not all individuals can be included in the study. The sample should be made independently, ensuring that the selection of one does not affect the inclusion or exclusion of the other [5]. Clinical

* Corresponding author: Kalpesh Khutade

practice involves sampling specific patients or multiple centers, rather than sampling the entire universe. Researchers should exercise caution when generalizing outcomes, as tertiary care hospitals may have more risk factors than primary centers, where patients with less severe disease are managed. Researchers must disclose the study area details and study period to readers, as it helps to understand population characteristics and highlights the relevance of the study to the current period [6].

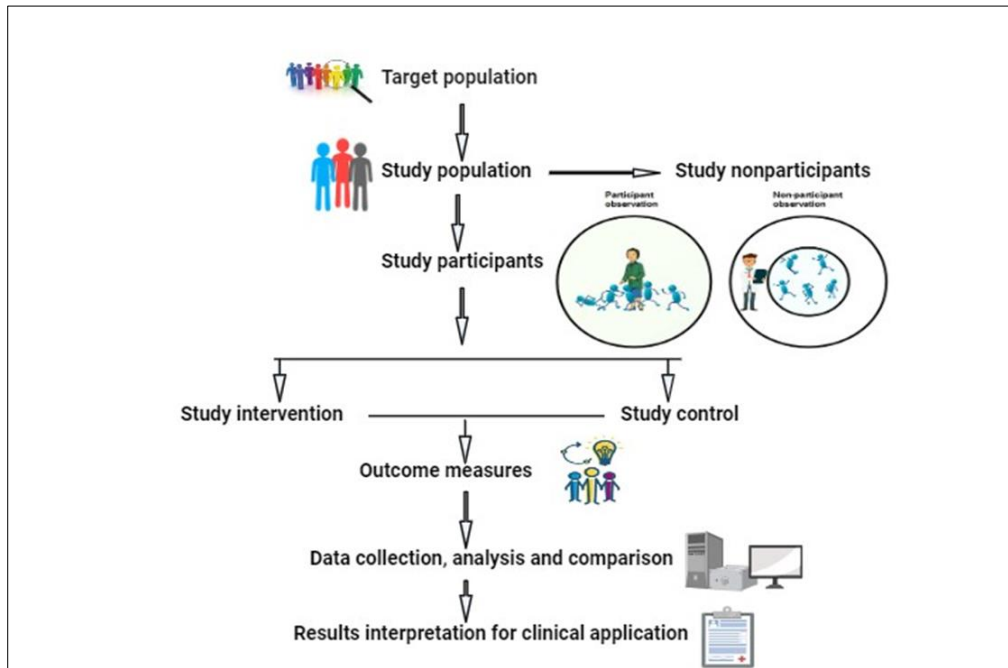


Figure 1 The study flow in an experimental design

The sample size must be predetermined, analytically approached, and sufficiently large to represent the population accurately. Larger samples may lead to resource wastage, missed treatment effects due to population heterogeneity, and time-consuming research, while too small samples may not provide suitable answers. The sample size is determined by several factors, including the clinical hypothesis, primary endpoint, study design, Type I and II error probability, power, and minimum clinically important treatment difference. The sample size calculation should consider the attrition of patients [7].

3. The effects of a randomized controlled trial on the outcomes of a single treatment

The study design is crucial for obtaining the most accurate and reliable estimates of the intervention outcomes. Study design selection is influenced by factors such as objectives, therapeutic area, treatment comparison, outcome, and trial phase [8]. The study design can be broadly classified into quantitative methods, including observational, descriptive, analytical, cross-sectional, experimental, and qualitative methods, including case reports, case series, surveys, randomized controlled trials, and quasi-experiments. Analytical observational studies are recommended for studying causality to avoid risk to subjects, whereas experimental studies are more suitable for clinical drugs or techniques [9]. The treatments in the Randomized Controlled Trial (RCT) were conducted concurrently, meaning that both active and control interventions occurred simultaneously. This study may employ a parallel group design in which the treatment and control groups are assigned to different individuals. The process involved comparing a placebo group or gold-standard intervention with a newer agent or technique. A matched-design RCT involves randomization between pairs, while a cross-over study design involves administering multiple treatments sequentially to the same subject, each acting as its own control. Research should consider the 'carryover effect' of previous interventions and ensure a suitable washing period [10]. The cohort study design involves tracking subjects with disease/symptoms or those without a study variable for a specific period. This study investigated the prevalence of the disease using surveys, validating instruments, tools, and questionnaires. Qualitative research is a study design that investigates health-related issues in a population through description, exploration, and explanation [11].

4. Use of an intervention: what are the use principles of analgesics?

Control is necessary to avoid self-remitting diseases, Hawthorne effects, placebo effects, confounder effects, co-intervention, and regression to the mean phenomena. The control could be a placebo, no treatment, different doses, regimens, interventions, or standard/gold treatment. Avoiding routine care for placebo is unethical, as it would be unethical to administer analgesics to a control group to study the analgesic regimen [12]. The recommendation was to maintain the standard of care, including providing routine analgesics, even in the control group. The use of a placebo or no treatment is considered when no proven intervention exists, or when a placebo is needed to assess the efficacy or safety of an intervention without serious or irreversible harm. The study must specify comparisons among different groups. Comparisons can indicate superiority, non-inferiority, or equivalence among the groups. The superiority trials either showed superiority to a placebo in a placebo-controlled trial or to an active control treatment [13]. Non-inferiority trials would demonstrate that an intervention's efficacy is comparable to that of active comparative treatment. Equivalence trials have shown that clinically unimportant differences between two or more interventions can be resolved by either technique or drug.

5. The use of objectively defined study tools

The study tools like measurement scales, questionnaires, and scoring systems should be defined objectively. The use of these tools must be validated and appropriated by the research staff to prevent any potential bias. The tools should be straightforward and easily comprehensible to all participants in the study [6,14].

5.1. Inclusion/exclusion criteria

Clinical research requires the selection of a specific group of relatively homogeneous patients. The study sample's inclusion or exclusion criteria determine who can be included or excluded. The inclusion criteria ensure a consistent, reliable, uniform, and objective identification of the study population. The exclusion criteria refer to factors or characteristics that render the selected population ineligible for the study. Factors can impact the outcome parameter, such as excluding patients with liver disease if coagulation parameters affect the outcome [11,13,15].

5.2. Variables: primary and secondary

Variables are the specific characteristics being studied, and a precise and objective definition for measuring these characteristics is necessary. The data should be measurable, interpretable, sensitive to the study objective, and clinically relevant. The primary or secondary variables of the study can be related to efficacy, safety, and quality of life [7,16]. The primary endpoint, typically one, provides the most relevant, reliable, and convincing evidence related to the aim and objective, forming the basis for formulating a research question/hypothesis. The sample size was determined by considering the clinically relevant and important treatment benefits. Secondary endpoints refer to objectives indirectly related to the primary objective, such as associated or adverse effects, and may be related to the intervention. The measurement timing of the variables must be defined beforehand, typically at screening, baseline, and trial completion [10,17]. The study endpoint parameter, either clinical or surrogate, directly impacts the clinical implications of the intervention's beneficial outcome. The surrogate endpoint, often measured in terms of laboratory or physical signs, is indirectly linked to patient clinical benefit and serves as a substitute for a clinically meaningful endpoint. Surrogate endpoints are more convenient, easily measurable, repeatable, and faster than their original counterparts [3,15,18,].

6. Sampling techniques

6.1. Randomization

Randomization is a method used to randomly assign individuals to one of the study arms. Randomization is a fundamental assumption in statistical analysis, aiming to enhance statistical power, particularly in subgroup analyses, and minimize selection and allocation bias. This results in the equal distribution of all characteristics, whether measured or non-measured, visible or invisible, and known or unknown, into the groups. Randomization employs various strategies based on the study design and outcome [19].

6.1.1. Probability sampling

- Simple/unrestricted: The sampling method ensures equal chance for each individual in a small, homogenous population using methods such as lottery, random table, or computer-generated data.

- Stratified: This method divides a non-homogenous population into homogenous groups (strata), randomly drawing samples from each stratum and ensuring similar characteristics across study groups through equal or proportional allocation.
- Systematic: This method is employed when a complete and up-to-date sampling frame is available, with the first unit selected randomly, and the rest automatically chosen according to a pre-designed pattern.
- Cluster: The population is divided into distinct units known as clusters, which are then surveyed to identify and classify them. The investigation included every unit in the chosen clusters.
- Multistage: This applies to extensive national surveys. Random sampling was used for step-by-step sampling. Subsampling was performed within the chosen clusters. This type of procedure is known as multistage sampling, if it is repeated in multiple stages.
- Multiphase: Two-phase sampling was used to collect data from a subsample of the units that made up the original sample, in addition to data collected from the sample as a whole. Multiphase sampling is a term used when three or more phases are used.

6.1.2. Non-probability sampling

This method does not provide every member of the population with an equal or non-zero chance of being chosen for the sample [19,20].

- Convenience: Sampling was carried out according to the investigator's convenience, that is, readily available.
- Purposive/judgemental/selective/subjective: The investigator uses their judgment to select the sample.
- Quota: This is carried out by the interviewer's assessment based on a few predetermined characteristics such as sex and physical status.

6.2. Allocation concealment

Allocation concealment is a method that keeps the random assignment generator unaware of the person's assigned arm. This strategy prevents ascertainment or selection bias, preventing researchers from excluding certain categories as lesser-sicker patients from a specific group based on an outcome. The selective recruitment method could either underestimate or overestimate the intervention effect based on the severity of the disease in the treatment group. The study's randomization should be performed by an independent individual who is not involved in the study's conduct or monitoring, ensuring the allocation remains hidden from the investigator. The randomization list is kept confidential through various methods of allocation concealment [17,21].

- Central randomization: A centrally independent authority performs randomization and communicates with investigators via telephone, email, or fax.
- Pharmacy control: The pharmacy provides coded drugs for use.
- Sequentially numbered containers: The use of identical containers that are equal in weight, similar in appearance, and tamper-proof is crucial.
- Sequentially numbered, opaque, sealed envelopes: Randomized numbers are stored in opaque envelopes ready for immediate intervention, making this a common and straightforward method.

6.3. Blinding/masking

Blinding is a technique used to assign study subjects to groups that are not easily identifiable by participants, investigators, evaluators, or statisticians to prevent bias. The intervention and standard or placebo treatment appear identical, but blinding differs from allocation concealment. Allocation concealment is performed before treatment, while blinding is done during and after the initiation of treatment. Blinding may not be feasible in situations like study drugs with different formulations or medical versus surgical interventions. Sham blocks or needling in subjects may be ethically questionable, so outcome measurement should be objective to avoid bias and blind the masked party. The research manuscript should detail the blinding process, including the individual who was blinded after being assigned to interventions and the specific technique used. Blinding could be: [22,23].

- Unblinded: Randomization cannot be concealed by this process.
- Single-blind: A participant, investigator, or assessor keeps their identity confidential.
- Double-blind: Both the participants and the investigator maintained their anonymity.
- Triple-blind: The participant and the investigator both kept the data analysis blind.

7. Conclusion

Thorough comprehension of the methodology is crucial for achieving a reliable, consistent, and clinically acceptable outcome. The study plan, including all its components, must be designed and strictly adhered to during the execution of the study.

Compliance with ethical standards

Disclosure of conflict of interest



The authors declare that there is no competing interest.

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Author's short Biography

	<p>Kalpesh Khutade is a pursuing Ph.D. candidate in the Microbiology Department of Sandip University, Nashik. He has a B.Sc. degree in microbiology (2012) and M.Sc. degree in microbiology (2015). His research involves a comparative evaluation of loop-mediated isothermal amplification (LAMP) and conventional microscopy in the diagnosis of pulmonary tuberculosis. He currently works as a microbiology Laboratory In-charge at the Vedanta Institute of Medical Sciences and Research Center</p>
	<p>Nisha Kumari is a pursuing Ph.D. candidate in the Microbiology Department of Malwanchal, Indore. She has a B.Sc. degree in Life Science (2016) and M.Sc. degree in Medical Microbiology (2020). Her research involves Extended spectrum beta-lactamase (ESBL) and AmpC producing Enterobacteriaceae in broiler Chicken and goat at Rama Medical College Hospital and Research Centre Kanpur. She currently works as a Tutor (Microbiology) at the Vedanta Institute of Medical Sciences and Research Center</p>