

Research Methods for Medical Graduates

Abhaya Indrayan



CRC Press

Taylor & Francis Group

Boca Raton London New York

CRC Press is an imprint of the
Taylor & Francis Group, an **informa** business

Contents

Preface	xi
Author	xiii
1 Basics of Medical Research	1
1.1 What Is Medical Research?	1
1.1.1 Medical Research and Empiricism	2
1.1.2 Types of Medical Research and the Scope of This Book	2
1.1.3 Levels of Medical Research	5
1.2 Uncertainties in Medical Research	8
1.2.1 Epistemic Uncertainties	8
1.2.2 Aleatory Uncertainties	11
1.2.3 Managing Uncertainties in Empirical Medical Research	14
1.3 Broad Steps in Medical Research	14
1.3.1 Pre-Investigation Steps	14
1.3.2 Investigation Steps	17
1.3.3 Post-Investigation Steps	18
1.4 Quality of Medical Research	21
1.4.1 What Qualifies Good Research?	21
1.4.2 Quality of a Good Researcher	21
1.4.3 Pleasures and Frustrations of Medical Research	22
2 The Topic of Medical Research	27
2.1 Selection of the Topic of Research	27
2.1.1 What Is a Problem?	27
2.1.2 Review of Literature and Databases, and Their Critique	29
2.2 Feasibility and Resources	34
2.2.1 Ethical Considerations	34
2.2.2 Resources	35
2.3 Objectives and Hypotheses	36
2.3.1 Broad and Specific Objectives	36
2.3.2 Hypotheses	37
3 Study Designs: An Overview	39
3.1 What Is a Design of an Empirical Study?	39
3.1.1 Elements of a Design	39
3.1.2 Types of Designs	40
3.2 Descriptive Studies	42
3.2.1 Sample Surveys and Their Designs	43
3.2.2 Case Studies and Case Series	44
3.2.3 Census	45
3.3 Analytical Studies	46
3.3.1 Choice of Strategy for Analytical Studies	46
3.3.2 Some Useful Terms and Concepts for Analytical Studies	47

3.4	Essentials of Intervention Studies	51
3.4.1	Medical Experiments	51
3.4.2	Clinical Trials	52
3.5	Essentials of Observational Studies	53
3.5.1	Prospective Studies	53
3.5.2	Retrospective Studies	54
3.5.3	Cross-Sectional Studies	54
3.6	Reliability and Validity of Designs, and Biases	54
3.6.1	Reliability of a Design	55
3.6.2	Validity of a Design	55
3.6.3	Biases in Medical Studies and Their Control	56
3.7	Where to Use Which Design?	63
3.7.1	Recommended Designs for Different Types of Research Questions	63
3.7.2	Levels of Evidence for Cause–Effect Relationships	63
4	Clinical Trials	67
4.1	Types of Clinical Trials	67
4.1.1	Therapeutic Trials – Efficacy and Safety	68
4.1.2	Clinical Trials for Diagnostic and Prophylactic Modalities	69
4.1.3	Field Trials for Screening, Prophylaxis, and Vaccines	70
4.1.4	Superiority, Equivalence, and Noninferiority Trials	72
4.1.5	Other Types of Clinical Trials	73
4.2	Basics of Clinical Trials	76
4.2.1	Arms of a Trial	76
4.2.2	Phases of a Clinical Trial	76
4.2.3	Randomization and Matching	78
4.2.4	Control Group in a Clinical Trial	82
4.3	Validity of a Clinical Trial	83
4.3.1	Selection of Participants	83
4.3.2	Blinding, Concealment of Allocation, and Masking	84
4.3.3	Compliance	87
4.3.4	Uncertainties in Clinical Trials	87
4.4	Choosing a Design for an Efficacy Trial	88
5	Observational Studies	91
5.1	Prospective Studies	91
5.1.1	Subjects in a Prospective Study	93
5.1.2	Potential Biases in Prospective Studies and Their Merits and Demerits	95
5.1.3	Cohort Studies	97
5.1.4	Longitudinal Studies	98
5.1.5	Repeated Measures Studies	99
5.2	Retrospective Studies	100
5.2.1	Case–Control Design	101
5.2.2	Selection of Cases and Controls	103
5.2.3	Merits and Demerits of Retrospective Studies	103
5.3	Cross-Sectional Studies	104
5.3.1	Merits and Demerits of Cross-Sectional Studies	105

5.4	Comparative Performance of Prospective, Retrospective, and Cross-Sectional Studies	106
5.4.1	Performance of a Prospective Study	108
5.4.2	Performance of a Retrospective Study	108
5.4.3	Performance of a Cross-Sectional Study	108
6	Assessment of Medical Factors	111
6.1	Intricacies of Assessment	111
6.1.1	Univariate and Multifactorial Assessments	112
6.1.2	Assessment in the Implementation Phase and the Results Phase.	112
6.2	Types of Medical Factors.	113
6.2.1	Distal and Proximal Factors	114
6.2.2	Physiological and Pathophysiological Factors.	116
6.2.3	Pathological Factors and Disease.	116
6.3	Assessment of Mortality, Duration, and Quality of Life	118
6.3.1	Assessment of Mortality	118
6.3.2	Quality of Life and Duration	119
7	Methodology of Data Collection	121
7.1	Types of Measurements.	122
7.1.1	Nominal, Metric, and Ordinal Measurements.	122
7.1.2	Other Types of Scales for Measurement	125
7.1.3	Continuous and Discrete Variables	126
7.2	Tools of Data Collection	127
7.2.1	Questionnaires, Schedules, and Proforma	127
7.2.2	Interview, Examination, and Investigation	130
7.3	Quality of Data	131
7.3.1	Errors in Medical Data.	131
7.3.2	Reliability, Validity, and Accuracy of Data	133
7.3.3	Other Aspects of Data Quality	135
7.4	Validity of the Tools.	136
7.4.1	Pilot Study and Pretesting.	136
7.4.2	Sensitivity and Specificity of Medical Tests	138
7.4.3	ROC Curves and Youden Index.	141
7.4.4	Predictivities and Prevalence	142
8	Sampling and Sample Size	147
8.1	Sampling Methods and Sampling for Descriptive Studies	148
8.1.1	Purposive Sampling (Nonrandom Methods).	149
8.1.2	Random Sampling	150
8.2	Sampling for Analytical Studies.	154
8.2.1	Sampling Methods in Observational Studies.	154
8.2.2	Sampling Methods in Clinical Trials.	155
8.3	Sampling and Nonsampling Errors.	156
8.3.1	Sampling Errors	156
8.3.2	Nonsampling Errors.	157

8.4	Sample Size	158
8.4.1	Sample Size for Descriptive Studies	160
8.4.2	Sample Size for Analytical Studies and Clinical Trials	160
	Appendix 1: Some Sample Size Formulas	164
9	Research Protocol	169
9.1	Structure of the Protocol	170
9.1.1	Title, Researchers, Supervisors, and Collaborators	171
9.1.2	Executive Summary	172
9.1.3	Main Body of the Protocol	172
9.1.4	Logistics and Appendices	172
9.2	Main Body of the Protocol	174
9.2.1	Specifics of the Content of the Main Body of the Protocol	174
9.2.2	Further Details of the Contents of the Main Body of the Protocol	178
10	Processing of Data	181
10.1	Collation of Data and Scrutiny	182
10.1.1	Uniformity of the Process of Data Collection	182
10.1.2	Data Validation	182
10.1.3	Master Chart and Data Entries	183
10.1.4	Indexes and Scores for Individual Subjects	184
10.2	Epidemiological Indices	186
10.2.1	Rates and Ratios	186
10.2.2	Prevalence and Incidence	187
10.2.3	Risk, Hazard, and Odds	188
10.3	Representative Summary Measures	192
10.3.1	Summary Measures for Quantitative Data	192
10.3.2	Summary Measures for Qualitative Data	195
10.4	Tabulation and Graphics	195
10.4.1	Categorization of Data and the Choice of Class Intervals	195
10.4.2	Types of Data Tables	196
10.4.3	Graphs and Diagrams	199
10.4.4	Statistical Distribution of Medical Measurements	204
10.4.5	Normal versus Abnormal Levels	206
11	Statistical Analysis	209
11.1	Confidence Intervals, <i>P</i> -Values, and Power	210
11.1.1	CI for Proportion and Mean	211
11.1.2	CI for Relative Risk and Odds Ratio	212
11.1.3	Statistical Significance, <i>P</i> -Value, and Power	212
11.2	Some Basic Statistical Tests	217
11.2.1	Tests for Qualitative Data	217
11.2.2	Tests for Quantitative Data	220
11.3	Relationships and Regressions	223
11.3.1	Dependent and Independent Variables	224
11.3.2	Basics of Logistic Regression	225
11.3.3	Ordinary Least Square Regression	227
11.3.4	Correlation and Agreement	229

11.4	Cause–Effect Relationships and Validation of Results	231
11.4.1	Evidence of Cause–Effect	231
11.4.2	Validation of the Findings.	234
11.5	Statistical Fallacies	236
11.5.1	Cherry-Picking the Statistical Indices	236
11.5.2	Fallacious Interpretation	238
11.5.3	Statistical Errors Can Cause Many Deaths.	240
12	Writing a Thesis or a Paper, and Oral Presentation	243
12.1	Effective Scientific Writing	243
12.1.1	Text Style	244
12.1.2	Tables	245
12.1.3	Illustrations	246
12.1.4	Format of a Manuscript (IMRaD).	247
12.2	Preliminaries of a Manuscript	248
12.2.1	Title	248
12.2.2	Authorship Credits	251
12.2.3	Keywords.	252
12.2.4	Abstract and Summary	252
12.3	Main Body of the Report	254
12.3.1	Writing a Suitable Introduction	254
12.3.2	Explaining Materials and Methods	255
12.3.3	Describing the Results	257
12.3.4	Discussion of Findings and Conclusion	260
12.4	End Features of a Report	262
12.4.1	Acknowledgment Ethics	262
12.4.2	Key Messages	263
12.4.3	References	263
12.4.4	Contribution of Authors and Conflict of Interest	265
12.4.5	Appendix.	265
12.5	Oral Presentation	265
12.5.1	Essentials of Effective Presentation	266
12.5.2	Poster Presentation.	269
13	Reporting Guidelines.	273
13.1	Guidelines for Reporting of Clinical Trials (CONSORT Statement).	273
13.2	Reporting of Observational Studies (STROBE Statement).	274
13.3	Reporting of Diagnostic Accuracy Studies (STARD Statement).	277
13.4	Guidelines for Reporting of Statistical Methods (Revised SAMPL Statement).	277
14	Reporting Ethics and Peer Reviews.	283
	Covering Letter.	284
14.1	Duplication	284
14.1.1	Duplicate Publication.	284
14.1.2	Plagiarism	285
14.1.3	Copyright and Permissions.	286

14.2	Conflicts and Reviews	286
14.2.1	Conflict of Interest	286
14.2.2	Peer Review	288
14.3	Confidentiality and Misreporting	290
14.3.1	Confidentiality	290
14.3.2	Misreporting	291
14.4	The Last Word.	292
Index		295

1

Basics of Medical Research

Research in any field is an enterprise that carries its own risks and benefits. One may make a heavy investment in terms of time, money, and expertise, yet the returns are not ensured in this endeavor. This is particularly so for medical research where we deal with unpredictable human beings and vitals such as health and life are at stake. First-time research is daunting anyway, but more so in medicine. Let us first understand what medical research is and what it is about in our context, so that the contents of this book are properly demarcated. This chapter gives an overview of medical research endeavors, including the pre-eminent role of empiricism, the dominance of uncertainties, broad steps, and the essential ingredients of good research. This would help in maintaining high standards in the research process so that the findings are believable and replicable. Details of all these aspects are provided in the subsequent chapters.

1.1 What Is Medical Research?

Research is discovery of new facts, enunciation of new principles, or fresh interpretation of the known facts or principles. It is an attempt to reveal to the world something that was either never thought of, or was in the domain of the conjectures – at best being looked at with suspicion. It is a systematic investigation to develop or contribute to generalizable knowledge. Research is a step in the relentless search for truth – it is an organized and systematic approach to finding answers to the intriguing questions. The basic function of research is to answer the why and how of a phenomenon, but searching for answers to questions such as what, when, how much, is also part of research endeavors. All these questions have relevance to any discipline, but medicine seems to have special appetite for such enquiries. The purpose of medical research is to learn how systems in the human body work, why we get sick, and how to get back to health and stay fit. It is a logical process to better understand the etiology, pathophysiology, diagnosis, therapy, and prognosis of health and diseases. Research is the very foundation of improved medical care. It can also provide evidence for policies and decisions on health development at the community level.

Besides the core activities just mentioned, sometimes an established regimen is used in a new setting or on a new kind of subject to test its applicability to the new environment. This kind of confirmatory work is not hard-core research, but is accepted for graduate

thesis because the objective there is training in research methodology and new results if any are considered bonus. A large number of medical theses are based on such confirmatory research.

Much of human biology is still speculative, and its interaction with the environment is intricate. Thus, medical science has enormous potential for useful research. At the same time it has its own risks. This is illustrated by the reports questioning established modalities. Tamoxifen, a selective estrogen-modifying agent and a popular breast cancer therapy for women, was found to carry an increased risk of endometrial cancer. Menopausal women who took estrogen for a long time were found to be at higher risk of getting ovarian cancer. Arthroscopic surgery for osteoarthritis of the knee was found to be a useless procedure. A high level of cholesterol is no longer considered as much a risk as it used to be. These are not isolated examples. There are many instances when established medical practices were overturned. Some recent advances have indeed been bivalent – potentially useful as well as potentially harmful. As discussed later in this chapter, this happens because most of modern medical research is empirical. It depends on the interpretation of what we observe, and neither observations nor their interpretation are infallible.

1.1.1 Medical Research and Empiricism

Medicine is a delicate science because it is concerned with vitalities of life such as health, disease, and death. Thus, it brooks no error. Ironically, no theories are available that can make it infallible. There are no lemmas and no theorems, and it must depend on evidence provided by observations and experience. Medicine is largely an inductive science and has very little space, if any, for deductive methods. It is individualized yet participatory. If a treatment regimen has worked in Mr. Somebody and nine others of his clan, there is a high likelihood that it would also work in the 11th person of that type. The past experience and present evidence provide an insight into the future. Such empiricism (Box 1.1) is the backbone of medical science. In dealing with a new case, or an old case with a new set of conditions, past knowledge and experience are applied, and it is hoped that they will also work in the new setup. Often they do, but sometimes not. There is no assurance. Miscues cited earlier are examples of such errors.

Empiricism is often contrasted with rationalism. Rational knowledge comes from the exploration of concepts, deduction, intuition, and revelation. For these, sensual experience is not necessary. However, it can be argued that all these also initially come from primary experiences. Empiricists argue that the knowledge we cannot sense does not exist – it could be just a guess or a presumption.

Without entering further into this debate, let us emphasize that empiricism and rationalism are complementary to each other for expansion of knowledge. This is more so in the context of medical research because much of it is on cause and effect. Mental illumination stipulated in theories may provide a clue to what may be really going on, but this needs support from actual observations. Only then can you hope to convince colleagues to accept your theory. Thus, most medical research has no escape from evidence base and empirical process. This book is restricted to the data-based research that is tangible and based on experience rather than intuition.

1.1.2 Types of Medical Research and the Scope of This Book

Medical research encompasses a whole gamut of endeavors that ultimately help to improve the health of people. Although nomenclature exists, such as qualitative and quantitative research, and public health and clinical research, functionally it can be divided into

BOX 1.1 EMPIRICISM AND RATIONALISM

Two basic forms of expansion of knowledge are empiricism and rationalism. Empiricism is based on induction from sensual learning; it is based on observations and experience as these arise from our senses. These observations and experience form what we call the evidence, and require that we do our best with whatever we have. Empirical evidence could arise from experiments, trials, natural occurrences, experiences, records, and such other sources. It refers to the actual facts as currently present or occurred in the past. You can see that empiricism emphasizes the tentative and probabilistic nature of knowledge. In contrast, mathematics and some other physical sciences are based on theories and theorems that are considered rational. For example, we postulate that the numbers that do not divide by any other number except 1 and themselves are prime, and deduce that 3 and 7 are two prime numbers less than 8. Such arguments are deductive and not empirical. Deductive science holds that the mind can directly perceive truth without going through the process of sensual experience.

Empiricism has no conflict with rationalism. The observations must stand up to the reason, and should have an adequate rational explanation. After all, it is the logic of reasoning that separates humans from other species. Research results are more acceptable when the accompanying evidence is compelling, stands to reason, and inspires confidence. Without logic, research is reduced to storytelling.

BOX 1.2 EVIDENCE ANALYSIS AND SYNTHESIS

The kind of medical research discussed in this book depends mostly on the analysis of evidence from various sources. The objective of this analysis is to identify clear signals emanating from the varying and sometimes conflicting evidence from the study subjects. When these signals conform with one another, clear conclusions can be drawn.

There is another type of medical research that is very popular and very effective. This is collecting diverse evidence from various studies (not individual subjects) and synthesizing it to get a holistic picture after resolving any conflicts. Review articles and meta-analyses appearing in medical journals are of this type. The discussion section of a master's thesis, doctoral dissertation, or a research paper also tries to do such synthesis, although this is limited to integrating your findings with the results of others. Methods for research synthesis are not included in this text.

basic and applied types. **Basic research**, also sometimes termed “pure research,” involves advancing the knowledge base without any specific focus on its application. The results of such research are utilized sometime in the future when that new knowledge is required. In medicine, basic research is generally done at the cellular level for studying various biological processes. Although this kind of research can provide a radical breakthrough, this book is not adequate for this kind of research. **Applied research**, on the other hand, is oriented to an existing problem. Applied medical research could be on the diagnostic and therapeutic modalities, agent–host–environment interactions, or health assessments, whether based on evidence analysis or synthesis (Box 1.2).

Primary and Secondary Research

Applied medical research can be classified into two major categories, although this is not a universally accepted classification. The first category can be called primary research and includes analytical studies such as case-control studies, laboratory experiments, and clinical trials. It also includes descriptive studies such as surveys, case series, and census. The second category is secondary research, which is quite common these days, and includes meta-analysis, decision analysis (risk analysis and decision theory), operations research (prioritization, optimization, simulation, etc.), evaluation of health systems (assessment of achievements and shortcomings), economic analysis (cost-benefit, cost-effectiveness, etc.), and qualitative research (focus group discussion). This text is confined to the methods used in primary research (Figure 1.1), but does not contain specialized methods required for pharmacokinetic and toxicological studies.

This book is designed to provide a holistic picture of the methodology of primary research that still forms the bulk of modern medical research. The text is for basic methods only and would be adequate for most research that is required to be collated as a master's thesis or doctoral dissertation, and for other such small-scale endeavors. Advanced methods would be different for, say, cancer research than for tuberculosis research and for a drug trial than for behavioral research. For such focused research, particularly if it is on a large scale, consult other relevant reference books and material.

The book describes all steps of primary medical research in simple language. We hope that this will help emerging scientists to learn the concepts and principles of designing and conducting such a research project with precision. It describes methods for formulating a research problem and setting objectives, for reviewing the existing literature and data, for identifying uncertainties, for designing the study to handle these uncertainties, for collection and collation of evidence, for measuring uncertainties, for assessing the antecedents and outcomes, for statistical analysis of data including significance and

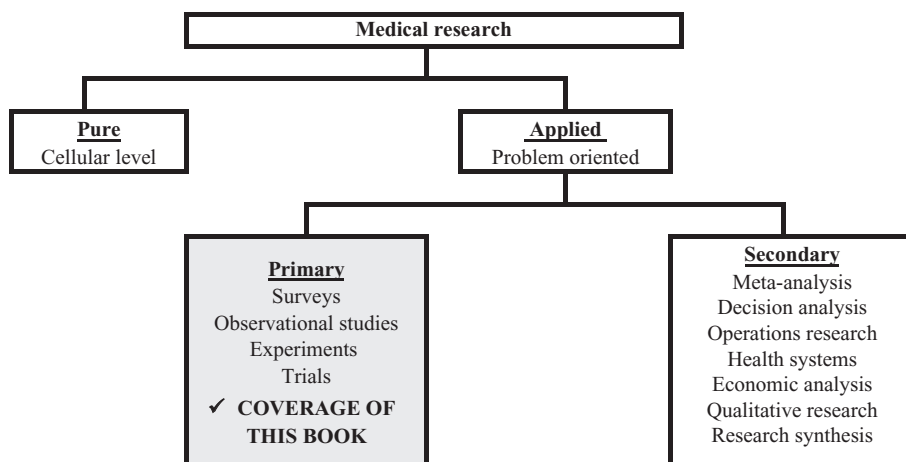


FIGURE 1.1

Types of medical research and coverage of this book.