ORIGINAL ARTICLE

Types of Study in Medical Research

Part 3 of a Series on Evaluation of Scientific Publications

Bernd Röhrig, Jean-Baptist du Prel, Daniel Wachtlin, Maria Blettner

SUMMARY

__Background:__ The choice of study type is an important aspect of the design of medical studies. The study design and consequent study type are major determinants of a study's scientific quality and clinical value.

__Methods:__ This article describes the structured classification of studies into two types, primary and secondary, as well as a further subclassification of studies of primary type. This is done on the basis of a selective literature search concerning study types in medical research, in addition to the authors' own experience.

__Results:__ Three main areas of medical research can be distinguished by study type: basic (experimental), clinical, and epidemiological research. Furthermore, clinical and epidemiological studies can be further subclassified as either interventional or noninterventional.

__Conclusions:__ The study type that can best answer the particular research question at hand must be determined not only on a purely scientific basis, but also in view of the available financial resources, staffing, and practical feasibility (organization, medical prerequisites, number of patients, etc.).   Dtsch Arztebl Int 2009; 106(15): 262–8
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__Key words: study type, basic research, clinical research, epidemiology, literature search__

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The quality, reliability and possibility of publishing a study are decisively influenced by the selection of a proper study design. The study type is a component of the study design (see the article "Study Design in Medical Research") and must be specified before the study starts. The study type is determined by the question to be answered and decides how useful a scientific study is and how well it can be interpreted. If the wrong study type has been selected, this cannot be rectified once the study has started.

After an earlier publication dealing with aspects of study design, the present article deals with study types in primary and secondary research. The article focuses on study types in primary research. A special article will be devoted to study types in secondary research, such as meta-analyses and reviews. This article covers the classification of individual study types. The conception, implementation, advantages, disadvantages and possibilities of using the different study types are illustrated by examples. The article is based on a selective literature research on study types in medical research, as well as the authors' own experience.

Classification of study types

In principle, medical research is classified into primary and secondary research. While secondary research summarizes available studies in the form of reviews and meta-analyses, the actual studies are performed in primary research. Three main areas are distinguished: basic medical research, clinical research, and epidemiological research. In individual cases, it may be difficult to classify individual studies to one of these three main categories or to the subcategories. In the interests of clarity and to avoid excessive length, the authors will dispense with discussing special areas of research, such as health services research, quality assurance, or clinical epidemiology. *Figure 1* gives an overview of the different study types in medical research.
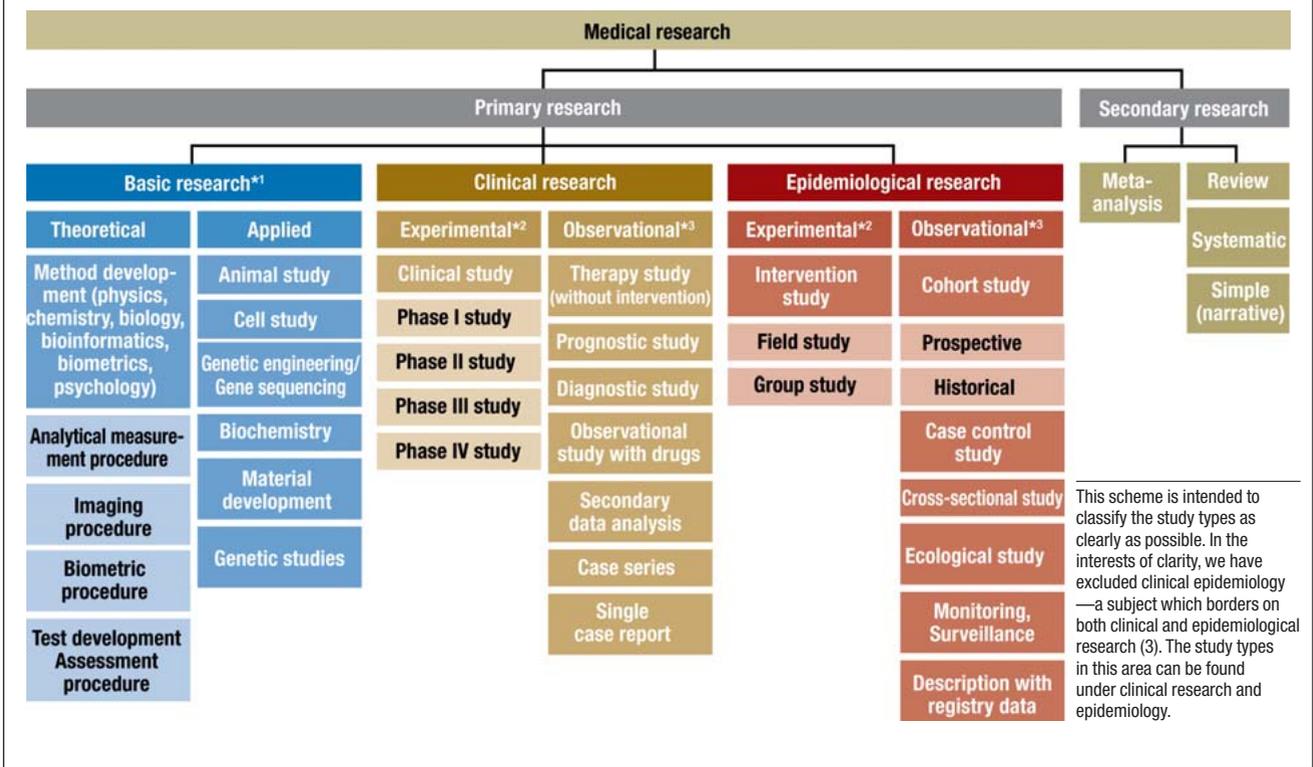
Basic research

Basic medical research (otherwise known as experimental research) includes animal experiments, cell studies, biochemical, genetic and physiological investigations, and studies on the properties of drugs and materials. In almost all experiments, at least one

FIGURE 1

Classification of different study types

*1, sometimes known as experimental research; *2, analogous term: interventional; *3, analogous term: noninterventional or nonexperimental

independent variable is varied and the effects on the dependent variable are investigated. The procedure and the experimental design can be precisely specified and implemented (1). For example, the population, number of groups, case numbers, treatments and dosages can be exactly specified. It is also important that confounding factors should be specifically controlled or reduced. In experiments, specific hypotheses are investigated and causal statements are made. High internal validity (= unambiguity) is achieved by setting up standardized experimental conditions, with low variability in the units of observation (for example, cells, animals or materials). External validity is a more difficult issue. Laboratory conditions cannot always be directly transferred to normal clinical practice and processes in isolated cells or in animals are not equivalent to those in man (= generalizability) (2).

Basic research also includes the development and improvement of analytical procedures—such as analytical determination of enzymes, markers or genes—, imaging procedures—such as computed tomography or magnetic resonance imaging—, and gene sequencing—such as the link between eye color and specific gene sequences. The development of biometric procedures—such as statistical test procedures, modeling and statistical evaluation strategies—also belongs here.

Clinical studies

Clinical studies include both interventional (or experimental) studies and noninterventional (or observational) studies. A clinical drug study is an interventional clinical study, defined according to §4 Paragraph 23 of the Medicines Act [Arzneimittelgesetz; AMG] as "any study performed on man with the purpose of studying or demonstrating the clinical or pharmacological effects of drugs, to establish side effects, or to investigate absorption, distribution, metabolism or elimination, with the aim of providing clear evidence of the efficacy or safety of the drug."

Interventional studies also include studies on medical devices and studies in which surgical, physical or psychotherapeutic procedures are examined. In contrast to clinical studies, §4 Paragraph 23 of the AMG describes noninterventional studies as follows: "A noninterventional study is a study in the context of which knowledge from the treatment of persons with drugs in accordance with the instructions for use specified in their registration is analyzed using epidemiological methods. The diagnosis, treatment and monitoring are not performed according to a previously specified study protocol, but exclusively according to medical practice."

The aim of an interventional clinical study is to compare treatment procedures within a patient population,

which should exhibit as few as possible internal differences, apart from the treatment (4, e1). This is to be achieved by appropriate measures, particularly by random allocation of the patients to the groups, thus avoiding bias in the result. Possible therapies include a drug, an operation, the therapeutic use of a medical device such as a stent, or physiotherapy, acupuncture, psychosocial intervention, rehabilitation measures, training or diet. Vaccine studies also count as interventional studies in Germany and are performed as clinical studies according to the AMG.

Interventional clinical studies are subject to a variety of legal and ethical requirements, including the Medicines Act and the Law on Medical Devices. Studies with medical devices must be registered by the responsible authorities, who must also approve studies with drugs. Drug studies also require a favorable ruling from the responsible ethics committee. A study must be performed in accordance with the binding rules of Good Clinical Practice (GCP) (5, e2–e4). For clinical studies on persons capable of giving consent, it is absolutely essential that the patient should sign a declaration of consent (informed consent) (e2). A control group is included in most clinical studies. This group receives another treatment regimen and/or placebo—a therapy without substantial efficacy. The selection of the control group must not only be ethically defensible, but also be suitable for answering the most important questions in the study (e5).

Clinical studies should ideally include randomization, in which the patients are allocated by chance to the therapy arms. This procedure is performed with random numbers or computer algorithms (6–8). Randomization ensures that the patients will be allocated to the different groups in a balanced manner and that possible confounding factors—such as risk factors, comorbidities and genetic variabilities—will be distributed by chance between the groups (structural equivalence) (9, 10). Randomization is intended to maximize homogeneity between the groups and prevent, for example, a specific therapy being reserved for patients with a particularly favorable prognosis (such as young patients in good physical condition) (11).

Blinding is another suitable method to avoid bias. A distinction is made between single and double blinding. With single blinding, the patient is unaware which treatment he is receiving, while, with double blinding, neither the patient nor the investigator knows which treatment is planned. Blinding the patient and investigator excludes possible subjective (even subconscious) influences on the evaluation of a specific therapy (e.g. drug administration versus placebo). Thus, double blinding ensures that the patient or therapy groups are both handled and observed in the same manner. The highest possible degree of blinding should always be selected. The study statistician should also remain blinded until the details of the evaluation have finally been specified.

A well designed clinical study must also include case number planning. This ensures that the assumed therapeutic effect can be recognized as such, with a previously

FIGURE 2
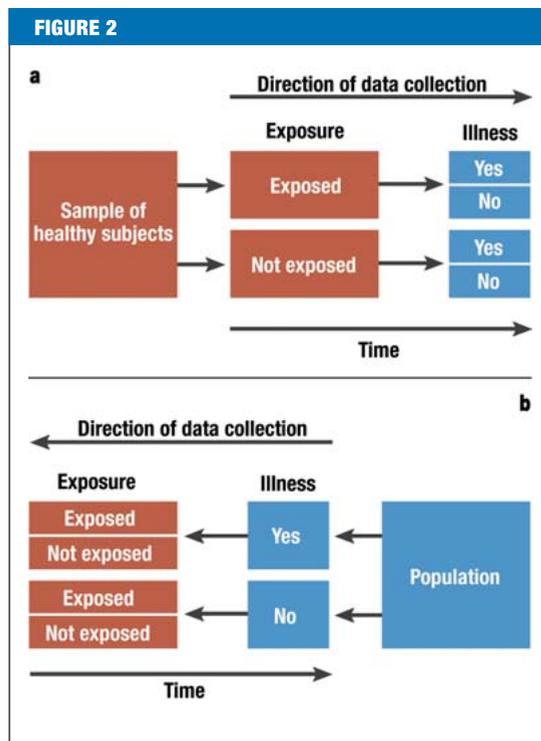
Graphical depiction of a prospective cohort study (simplest case [2a]) and a retrospective case control study (2b)

TABLE 1

Specially well suited study types for epidemiological investigations (taken from [e8])

Study objective	Study type
Study of rare diseases such as cancers	Case control studies
Study of rare exposure, such as exposure to industrial chemicals	Cohort studies in a population group in which there has been exposure (e.g. industrial workers)
Study of multiple exposures, such as the combined effect of oral contraceptives and smoking on myocardial infarction	Case control studies
Study of multiple end points, such as mortality from different causes	Cohort studies
Estimate of the incidence rate in exposed populations	Exclusively cohort studies
Study of covariables which change over time	Preferably cohort studies
Study of the effect of interventions	Intervention studies

specified statistical probability (statistical power) (4, 6, 12).

It is important for the performance of a clinical trial that it should be carefully planned and that the exact clinical details and methods should be specified in the study protocol (13). It is, however, also important that the implementation of the study according to the protocol, as well as data collection, must be monitored. For a first class study, data quality must be ensured by double data entry, programming plausibility tests, and evaluation by a biometrician. International recommendations for the reporting of randomized clinical studies can be found in the CONSORT statement (Consolidated Standards of Reporting Trials, www.consort-statement.org) (14). Many journals make this an essential condition for publication.

For all the methodological reasons mentioned above and for ethical reasons, the randomized controlled and blinded clinical trial with case number planning is accepted as the gold standard for testing the efficacy and safety of therapies or drugs (4, e1, 15).

In contrast, noninterventional clinical studies (NIS) are patient-related observational studies, in which patients are given an individually specified therapy. The responsible physician specifies the therapy on the basis of the medical diagnosis and the patient's wishes. NIS include noninterventional therapeutic studies, prognostic studies, observational drug studies, secondary data analyses, case series and single case analyses (13, 16). Similarly to clinical studies, noninterventional therapy studies include comparison between therapies; however, the treatment is exclusively according to the physician's discretion. The evaluation is often retrospective. Prognostic studies examine the influence of prognostic factors (such as tumor stage, functional state, or body mass index) on the further course of a disease. Diagnostic studies are another class of observational studies, in which either the quality of a diagnostic method is compared to an established method (ideally a gold standard), or an investigator is compared with one or several other investigators (inter-rater comparison) or with himself at different time points (intra-rater comparison) (e1). If an event is very rare (such as a rare disease or an individual course of treatment), a single-case study, or a case series, are possibilities. A case series is a study on a larger patient group with a specific disease. For example, after the discovery of the AIDS virus, the Center for Disease Control (CDC) in the USA collected a case series of 1000 patients, in order to study frequent complications of this infection. The lack of a control group is a disadvantage of case series. For this reason, case series are primarily used for descriptive purposes (3).

Epidemiological studies
The main point of interest in epidemiological studies is to investigate the distribution and historical changes in the frequency of diseases and the causes for these. Analogously to clinical studies, a distinction is made between experimental and observational epidemiological studies (16, 17).

Interventional studies are experimental in character and are further subdivided into field studies (sample from an area, such as a large region or a country) and group studies (sample from a specific group, such as a specific social or ethnic group). One example was the investigation of the iodine supplementation of cooking salt to prevent cretinism in a region with iodine deficiency. On the other hand, many interventions are unsuitable for randomized intervention studies, for ethical, social or political reasons, as the exposure may be harmful to the subjects (17).

Observational epidemiological studies can be further subdivided into cohort studies (follow-up studies), case

TABLE 2

Advantages and disadvantages of observational studies (taken from [16])*

	Ecological study	Cross-sectional study	Case control study	Cohort study
Selection bias	N/A	2	3	1
Recall bias	N/A	3	3	1
Loss to follow-up	N/A	N/A	1	3
Confounding	3	2	2	1
Time required	1	2	2	3
Costs	1	2	2	3

1 = slight; 2 = moderate; 3 = high; N/A, not applicable.
*Individual cases may deviate from this pattern.

control studies, cross-sectional studies (prevalence studies), and ecological studies (correlation studies or studies with aggregated data).

In contrast, studies with only descriptive evaluation are restricted to a simple depiction of the frequency (incidence and prevalence) and distribution of a disease within a population. The objective of the description may also be the regular recording of information (monitoring, surveillance). Registry data are also suited for the description of prevalence and incidence; for example, they are used for national health reports in Germany.

In the simplest case, cohort studies involve the observation of two healthy groups of subjects over time. One group is exposed to a specific substance (for example, workers in a chemical factory) and the other is not exposed. It is recorded prospectively (into the future) how often a specific disease (such as lung cancer) occurs in the two groups *(figure 2a)*. The incidence for the occurrence of the disease can be determined for both groups. Moreover, the relative risk (quotient of the incidence rates) is a very important statistical parameter which can be calculated in cohort studies. For rare types of exposure, the general population can be used as controls (e6). All evaluations naturally consider the age and gender distributions in the corresponding cohorts. The objective of cohort studies is to record detailed information on the exposure and on confounding factors, such as the duration of employment, the maximum and the cumulated exposure. One well known cohort study is the British Doctors Study, which prospectively examined the effect of smoking on mortality among British doctors over a period of decades (e7). Cohort studies are well suited for detecting causal connections between exposure and the development of disease. On the other hand, cohort studies often demand a great deal of time, organization, and money. So-called historical cohort studies represent a special case. In this case, all data on exposure and effect

(illness) are already available at the start of the study and are analyzed retrospectively. For example, studies of this sort are used to investigate occupational forms of cancer. They are usually cheaper (16).

In case control studies, cases are compared with controls. Cases are persons who fall ill from the disease in question. Controls are persons who are not ill, but are otherwise comparable to the cases. A retrospective analysis is performed to establish to what extent persons in the case and control groups were exposed *(figure 2b)*. Possible exposure factors include smoking, nutrition and pollutant load. Care should be taken that the intensity and duration of the exposure is analyzed as carefully and in as detailed a manner as possible. If it is observed that ill people are more often exposed than healthy people, it may be concluded that there is a link between the illness and the risk factor. In case control studies, the most important statistical parameter is the odds ratio. Case control studies usually require less time and fewer resources than cohort studies (16). The disadvantage of case control studies is that the incidence rate (rate of new cases) cannot be calculated. There is also a great risk of bias from the selection of the study population ("selection bias") and from faulty recall ("recall bias") (see too the article "Avoiding Bias in Observational Studies"). *Table 1* presents an overview of possible types of epidemiological study (e8). *Table 2* summarizes the advantages and disadvantages of observational studies (16).

Discussion

Selecting the correct study type is an important aspect of study design (see "Study Design in Medical Research" in volume 11/2009). However, the scientific questions can only be correctly answered if the study is planned and performed at a qualitatively high level (e9). It is very important to consider or even eliminate possible interfering

factors (or confounders), as otherwise the result cannot be adequately interpreted. Confounders are characteristics which influence the target parameters. Although this influence is not of primary interest, it can interfere with the connection between the target parameter and the factors that are of interest. The influence of confounders can be minimized or eliminated by standardizing the procedure, stratification (18), or adjustment (19).

The decision as to which study type is suitable to answer a specific primary research question must be based not only on scientific considerations, but also on issues related to resources (personnel and finances), hospital capacity, and practicability. Many epidemiological studies can only be implemented if there is access to registry data. The demands for planning, implementation, and statistical evaluation for observational studies should be just as high for observational studies as for experimental studies. There are particularly strict requirements, with legally based regulations (such as the Medicines Act and Good Clinical Practice), for the planning, implementation, and evaluation of clinical studies. A study protocol must be prepared for both interventional and noninterventional studies (6, 13). The study protocol must contain information on the conditions, question to be answered (objective), the methods of measurement, the implementation, organization, study population, data management, case number planning, the biometric evaluation, and the clinical relevance of the question to be answered (13).

Important and justified ethical considerations may restrict studies with optimal scientific and statistical features. A randomized intervention study under strictly controlled conditions of the effect of exposure to harmful factors (such as smoking, radiation, or a fatty diet) is not possible and not permissible for ethical reasons. Observational studies are a possible alternative to interventional studies, even though observational studies are less reliable and less easy to control (17).

A medical study should always be published in a peer reviewed journal. Depending on the study type, there are recommendations and checklists for presenting the results. For example, these may include a description of the population, the procedure for missing values and confounders, and information on statistical parameters. Recommendations and guidelines are available for clinical studies (14, 20, e10, e11), for diagnostic studies (21, 22, e12), and for epidemiological studies (23, e13). Since 2004, the WHO has demanded that studies should be registered in a public registry, such as www.controlledtrials.com or www.clinicaltrials.gov. This demand is supported by the International Committee of Medical Journal Editors (ICMJE) (24), which specifies that the registration of the study before inclusion of the first subject is an essential condition for the publication of the study results (e14).

When specifying the study type and study design for medical studies, it is essential to collaborate with an experienced biometrician. The quality and reliability of the study can be decisively improved if all important details are planned together (12, 25).

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