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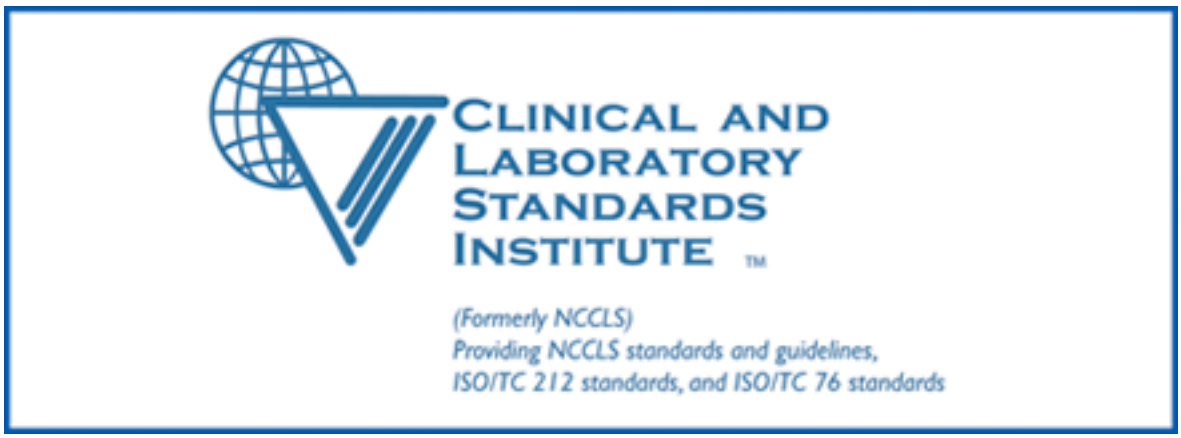
Studies to Evaluate Patient Outcomes; Approved Guideline



This guideline describes the essential issues in planning outcomes research, including resources needed, formulating a research question, validity and sources of error, feasibility, and ethical issues; addresses the design and implementation of a patient outcomes research plan, including study design, study subjects, measurements, interventions, and analysis; summarizes recommendations for reporting patient outcomes research; and includes definitions, references, and resources for those interested in planning, conducting, and using patient outcomes research.

A guideline for global application developed through the NCCLS consensus process.

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NCCLS...

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Studies to Evaluate Patient Outcomes; Approved Guideline

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Abstract

NCCLS document HS6-A—*Studies to Evaluate Patient Outcomes; Approved Guideline* provides an overview of patient outcomes studies and health services research to assist healthcare providers, managers of healthcare services, and others in planning, conducting, and reporting patient outcomes research. This guideline describes the essential issues in planning outcomes research, including resources needed, formulating a research question, validity and sources of error, feasibility, and ethical issues; addresses the design and implementation of a patient outcomes research plan, including study design, study subjects, measurements, interventions, and analysis; summarizes recommendations for reporting patient outcomes research; and includes definitions, references, and resources for those interested in planning, conducting, and using patient outcomes research.

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Foreword

A number of factors have converged to make efforts to monitor and improve the quality of health care increasingly important. Rapid changes in the organization and financing of services have led to unprecedented efforts to reduce the use and cost of services, while not adversely affecting either the delivery of services or patient outcomes. As the average lifespan of the population increases, the focus of medical care has shifted from the traditional role of providing treatment for acute care and the prevention of premature mortality to a role of helping people manage more chronic conditions. An increased interest in maintaining, prolonging, and improving the quality of life has prompted patients to want to be better informed about their care options. However, informed decision making requires that measures of patient outcomes are available and understood, and work, in addition to being cost effective.

Large variations in the way health care was practiced across the country became evident from studies done by Wennberg.[1] Importantly, these differences in practice did not lead to obvious differences in patient outcomes. In addition, research by Brooks on appropriateness of care[2] and Eddy on the poor quality of medical evidence[3] indicated that much of the care being provided was either unnecessary or inappropriate, regardless of the intensity of practice variation. Therefore, the assumed scientific basis for much of the established practice was called into question, and it was evident that studies were needed to determine which healthcare practices would be most effective and lead to better patient outcomes.

Recently, society has become increasingly concerned not only about the large variation in healthcare practice, but also with ensuring access to care and with reducing the costs of care. This has led to questions about whether care could be optimized by following specified protocols (i.e., practice guidelines). Several approaches have been developed to determine how best to improve patient outcomes, reduce variations in practice across the country, and contain costs. These include health services research, managed care, and national quality assurance activities.

Finally, researchers have begun to question the value of clinical trials as the gold standard to guide practice. The need to examine outcomes other than clinical endpoints, to look at outcomes of longer duration than those in a typical clinical trial, and to look at procedural interventions beyond drugs and clinical treatment has prompted the development of a whole new field to examine interventions applied to patients on a daily practical basis.

This document provides guidance to providers of healthcare services and manufacturers of healthcare products to assist with designing and conducting studies to evaluate patient outcomes. Using the tools provided in this document will help providers determine what works in their healthcare setting and to become the problem solvers, innovators, and quality improvement experts of the future. In addition, this document will assist those who wish to evaluate previously conducted studies by illustrating the strengths and weaknesses of various study designs. It can also help those involved in patient safety, quality improvement, and quality assurance activities to link their efforts more closely with improving patient outcomes, which is the ultimate goal of all of our efforts.

Key Words

Best practice, cost, effectiveness, efficiency, evidence-based medicine, health services research, patient outcomes, patient safety, processes, quality improvement, structure

Studies to Evaluate Patient Outcomes; Approved Guideline

1 Scope

This guideline can be applied to studies to evaluate patient outcomes by any service in a healthcare organization or manufacturer of a healthcare product. It includes essential elements to consider in either conducting studies, or evaluating previously conducted studies. The principles described are universal and can be used to make decisions about the most appropriate structure and processes to use for delivery of healthcare services. The document has been developed through the NCCLS consensus process and describes general criteria for conducting studies of patient outcomes. It is not intended to be a primer or manual for conducting research. There are several excellent books available for readers interested in more specific information about how to conduct a patient outcomes study, including information on qualitative and quantitative research methods (see the Additional References section).

The focus of this guideline is on primary studies in patient outcomes research. These include observational studies (surveys or cross-sectional studies, case-control studies, and cohort studies) and interventional studies (randomized controlled trials and nonrandomized studies).

The role of systematic overviews, meta-analyses, decision analyses, cost-effectiveness analyses, and simulations is described briefly.

2 Introduction

The guidance described in this document can be used to evaluate patient outcomes by anyone in the healthcare field. It is designed to meet the needs of both the providers of healthcare services, who are under increasing pressure to provide effective and efficient patient care, and the manufacturers of medical devices and kits, who are in an increasingly competitive market and must demonstrate the added value of their products. The techniques described provide the means that anyone in the healthcare field could use to answer basic questions about the quality and effectiveness of the services they provide, pay for, or oversee. In particular, these techniques should be useful to those who must find ways to evaluate and improve the quality of service they offer. Evaluation of the impact of changes in structure or processes on patient outcomes can help identify ways to reduce errors in processes and practices, to avoid mistakes, and to evaluate the validity of claims by others. Since patient outcomes is the ultimate measure of success or failure in health care, it is essential that those who work in the field know what works and what does not work in order to produce better patient outcomes.

2.1 Potential Impact of Outcomes Studies

Appropriately designed patient outcomes studies conducted at even a single institution can have a significant impact on local, regional, and even national policies, practices, and future health care. Advances in the field of outcomes research have progressed to the point that it is increasingly recognized that: (1) evidence, not opinion, should guide healthcare decisions; (2) more patient outcomes studies are needed to help determine the best way to deliver the benefits and avoid the risks of the complex, but technologically advanced healthcare system; (3) methods are available to conduct patient outcomes studies; and (4) such studies could lead to patient care alternatives that could provide better patient outcomes, sometimes at lower cost.

Properly conducted patient outcomes studies have the capacity to provide decision makers with the evidence they need to make changes in policies, procedures, and practices. Studies have many uses, but are most often applied in the following ways:

- to advocate changing customary practice to evidence-based practice;

- to evaluate technologies or procedures in a different or specific setting not previously studied;

- to evaluate the effect of economic or social issues on outcomes (Outcomes and effectiveness research seeks to understand the end results of particular healthcare practices and interventions. By linking the care people receive [taking into account their social and economic environment] with outcomes they experience, outcomes research becomes the key to developing better ways to monitor and improve the quality of care.);

- to develop clinical practice guidelines, which are systematically developed statements to assist practitioner and patient decisions about appropriate health care for specific clinical circumstances (The National Guidelines Clearinghouse (NGC) at http://www.guideline.gov is intended to make evidence-based clinical practice guidelines widely available to healthcare professionals.);

- to develop criteria for accreditation programs (For example, in the U.S., the National Committee for Quality Assurance (NCQA) HEDIS® (Healthplan Employers Data and Information Set) measures, the Joint Commission on Accreditation of Healthcare Organizations (JCAHO) ORYX program, and The Foundation for Accountability (FACCT) help identify and promote patient-oriented measures of healthcare quality.);

- to assist government programs with decisions about reimbursement and other policies;

- to determine whether the processes and practices we employ in our healthcare services are of the quality required to provide adequate and appropriate patient care;

- to improve patient safety (The critical issue of medical error and patient safety has received a great deal of attention as a result of the Institute of Medicine (IOM) report,[4] which estimated that as many as 98,000 patients in the United States die as the result of medical errors in hospitals each year. More studies are needed to determine how often medical errors occur and result in patient injury.);

- to evaluate the effectiveness of introduction of a new structure or standardized protocol (Healthcare organizations need to test the effectiveness of the transfer and application of systems-based best practices to reduce medical errors and improve patient safety. Such research will help identify high-risk patients or patient groups, providers, healthcare processes and settings, as well as develop generalizable methods for error reduction.);

- to find better ways to manage patient care (Quality management can be thought of as the broad umbrella that those responsible for the management of an organization place over the entire organization. This includes the policies, practices, and processes needed to ensure that the facility, the personnel, the technical aspects of the service, etc. meet the intended goals for patient care. Studies of patient outcomes assist efforts to improve the provision of services.); or

- to define the best practices in health care (The results of properly designed, conducted, and analyzed patient outcomes studies contribute to the body of evidence for best practices. The conscientious, explicit, and judicious use of current best evidence to make decisions has been termed "evidence-based medicine."[5])

2.2 The Need for a Guideline for Outcomes Research

In our present environment of limited healthcare resources, providers of patient care are often unprepared to provide or obtain data needed for decision making about ways to improve the quality or reduce the cost of the care they offer. They are even less able to demonstrate a difference in patient outcomes as a result

of an attribute of quality or clinical utility that they provide. This guide is intended to assist those involved in healthcare delivery or who manufacture devices used in healthcare delivery or associated services with the design, conduct, and assessment of patient outcomes studies. It describes the methods that can be used to collect the data and information needed to demonstrate an improvement in patient outcomes, with an emphasis on what can be practically accomplished by a single institution with limited resources or experience in research. Measuring what works in health care should lead naturally to a cycle of processes, where data provide information, which leads to the knowledge required for scientifically based decision making, leading to actions that enhance patient care.

3 Definitions

Alpha error – See definition of **Type I error**, below.

Autonomy – The right to choose one's own actions or course of life so long as doing so does not interfere unduly with the lives and actions of others; **NOTE:** Autonomy is the basis of the ethical value of respect for persons and respect for the subjects in research studies, and forms the basis of requirements for informed consent, protection of vulnerable subjects, and maintaining confidentiality of research data.[6]

Beneficence – The duty to do good and avoid harm to others; **NOTE:** The principle of beneficence requires that research design be scientifically sound and that the risks of the research be acceptable in relation to the likely benefits.[6]

Beta error – See definition of **Type II error**, below.

Between-group design – A study design in which comparisons are made between study subjects; **NOTES:** a) In observational studies, comparisons are made between two or more groups of study subjects with biological risk factors, environmental exposures, diagnoses, treatments, or use of health services; b) In experimental studies, comparisons are made between two or more groups of study subjects who are allocated, ideally at random, to clinical treatments or the use of specific health services.

Bias – **1)** Lack of validity; the degree to which a study fails to measure what it is designed to measure, due to deviation of results or inferences from the truth, or processes leading to such deviation; **2)** Any trend in the collection, analysis, interpretation, publication, or review of data that can lead to conclusions that are systematically different from the truth. Ways in which this deviation from the truth can occur include: a) Systematic (one-sided) variation of measurements from the true values (also known as "systematic error"); b) Variation of statistical summary measures (means, rates, measures of association, etc.) from their true values as a result of systematic variation of measurements, other flaws in data collection, or flaws in study design or analysis; c) Deviation of inferences from the truth as a result of flaws in study design, data collection, or the analysis or interpretation of results; d) A tendency of procedures (in study design, data collection, analysis, interpretation, review or publication) to yield results or conclusions that depart from the truth; e) Prejudice leading to the conscious or unconscious selection of study procedures that depart from the truth in a particular direction or to one-sidedness in the interpretation of results; **NOTE:** Many different types of study bias have been described,[7] including systematic distortion of the estimated intervention effect away from the "truth," caused by inadequacies in the design, conduct, or analysis of a trial.[8]

Blinding//masking – The practice of keeping the trial participants, care providers, those collecting data, and sometimes even those analyzing data unaware of which intervention is being administered to which participant; **NOTES:** a) Blinding is intended to prevent bias on the part of study personnel; b) A very common application is "double-blinding," in which participants, caregivers and investigators, and those collecting data are blinded to knowledge of the intervention that is administered; in "triple blinding" those persons assessing outcome and analyzing the outcomes are blinded to intervention assignment.[8]

Case-control study – Type of observational study design in which determination of outcome precedes determination of exposure; **NOTES:** a) In this study design, the relationship of an attribute of subjects (or their environment) to the occurrence of a disease or other outcome of interest is examined by comparing a group of persons having this outcome (cases) with a suitable control (comparison, reference) group. The two groups are compared with respect to how frequently the attribute is present, or if quantitative, the levels of the attribute in each of the two groups. In other words, the past history of exposure to a suspected *risk factor* is compared between "cases" and "controls." The controls are persons who resemble the cases in such respects as age and sex, but do not have the disease or outcome of interest; b) This study design starts after the occurrence of the outcome and looks back to the postulated causal factors. Cases and controls may be accumulated either retrospectively (i.e., from among subjects whose outcome and exposure status are already known) or prospectively (i.e., as each new case is determined, it is entered into the study).[7]

Chance – Random error.

Charges – The price of a service or amount billed an individual or third party, which may or may not be equal or even proportional to service costs[9]; **NOTE:** See also **Cost**.

Cohort study – Type of observational study design in which determination of exposure precedes determination of outcome; **NOTES:** a) In this study design, subsets of a defined population are identified who are, have been, or in the future may be exposed or not exposed, or exposed in different degrees, to a factor or factors hypothesized to influence the possibility of occurrence of a given disease or other outcome of interest; b) The main feature of cohort study is observation of large numbers over a long period (commonly years) with comparison of incidence rates in groups that differ in exposure levels. An essential feature of the method is observation of the population for a sufficient number of person-years to generate reliable incidence or mortality rates in the population subsets. This generally implies study of a large population, study for a prolonged period (years), or both. The denominator may be persons or person-time; c) Cohort studies may be conducted prospectively, as described above, or "retrospectively" as historical cohort studies. Such studies use existing records about the health or other relevant aspects of a population as it was at some time in the past and determines the current (or subsequent) status of members of this population with respect to the condition of interest.[7]

Confidence interval – The computed interval with a given probability (e.g., 95%) that the true value of a variable such as a mean, proportion, or rate, is contained within the interval.[7]

Confounding – **1)** A situation in which the effects of two processes are not separated; **NOTE:** The distortion of the apparent effect of an exposure on risk brought about by the association with other factors that can influence the outcome;[10] **2)** A situation in which the intervention effect is biased because of some difference between the comparison groups apart from the planned interventions, such as baseline characteristics, prognostic factors, or concomitant interventions; **NOTE:** For a factor to be a confounder, it must differ between the comparison groups and predict the outcome of interest.[8]

Cost – Expenses incurred in the provision of services or goods; **NOTE:** Many different kinds of costs are defined and used (see allowable, direct, indirect, and operating costs); charges, the price of a service or amount billed an individual or third party, may or may not be equal or even proportional to service costs.[9]

Cost-benefit analysis – An analytic method in which a program's cost is compared to the program's benefits for a period of time, expressed in dollars, as an aid in determining the best investment of resources; **NOTES:** a) For example, the cost of establishing an immunization service might be compared with the total cost of medical care and lost productivity which will be eliminated as a result of more persons being immunized; b) Cost-benefit analysis can also be applied to specific medical tests and treatments.[9]

Cost-effectiveness analysis (CEA) – **1)** This form of analysis seeks to determine the costs and effectiveness of an activity or to compare similar alternative activities to determine the relative degree to which they will obtain the desired objectives or outcomes; the preferred action or alternative is one that requires the least cost to produce a given level of effectiveness, or provides the greatest effectiveness for a given level of cost; **NOTE:** In the healthcare field, outcomes are measured in terms of health status;[7] **2)** A form of analysis that seeks to determine the costs and effectiveness of a medical intervention compared to similar alternative interventions to determine the relative degree to which they will obtain the desired health outcome(s); **NOTE:** Cost-effectiveness analysis can be applied to any of a number of standards such as median life expectancy or quality of life following an intervention.[9]

Cross-sectional study – A type of observational study that examines the relationship between diseases or other health-related characteristics, and other variables of interest as they exist in a defined population at one particular time; **NOTES:** a) The presence or absence of disease and the presence or absence of the other variables (or, if they are quantitative, their level) are determined in each member of the study population or in a representative sample at one particular time; b) The relationship between a variable and the disease can be examined: (1) in terms of the prevalence of disease in different population subgroups defined according to the presence or absence (or level) of the variables; and (2) in terms of the presence or absence (or level) of the variables in the diseased versus the nondiseased; c) Disease prevalence rather than incidence is normally recorded in a cross-sectional study; d) The temporal sequence of cause and effect cannot necessarily be determined in a cross-sectional study.[7]

Decision analysis – A derivative of operations research and game theory that involves identifying all available choices, and potential outcomes of each, in a series of decisions that have to be made about aspects of patient care—diagnostic procedures, therapeutic regimens, prognostic expectations; **NOTES:** a) Epidemiologic data play a large part in determining the probabilities of outcomes following each choice that has to be made; b) The range of choices can be plotted on a *decision tree*, and at each branch or decision node, the probabilities of each outcome that can be predicted are displayed; the decision tree thus portrays the choices available to those responsible for patient care and the probabilities of each outcome that will follow the choice of a particular action or strategy in patient care; c) The relative worth of each outcome is preferably described as a utility or quality of life, e.g., a probability of life expectancy or freedom from disability, often expressed as quality adjusted life years (QALYs).[7]

Direct cost – A cost which is identifiable directly with a particular activity, service, or product of the program experiencing the costs.[9]

Eligible population – The subset of the target population identified by an investigator who may be invited to participate in a prospective observational or experimental study design, or whose medical records will be identified by the investigator for review in a retrospective observational study design; **NOTES:** a) The eligible population should be representative of the target population about which the investigator intends to make valid inferences about the truth of the study hypotheses; b) Persons in the target population may not be eligible for a study because of ethical considerations of the risks in relation to benefits of participation in the study, study design issues related to efficiency, such as restricting the study to persons with more severe disease who are more likely to respond to interventions, or less likely to be lost to follow-up; c) Inferences about the target population made from the study findings in the eligible and enrolled population are suspect if the eligible and enrolled populations differ from the target population.

Enrolled population – **1)** The subset of the eligible and target population who are contacted, invited to participate, and actually give informed consent for participation in the study; **2)** The subset of the eligible and target population whose medical records are actually reviewed and from which information is actually obtained and included in the study; **NOTES:** a) The *enrolled population* is the *achieved sample size*; b) Inferences about the target population made from the study findings in the eligible and enrolled population are subject to bias if the eligible and enrolled populations differ from the target population.

Equipoise – **1)** An ethical basis for clinical research in which there is a state of genuine uncertainty on the part of the clinical investigator regarding the comparative therapeutic merits of each arm in a trial; **NOTES:** a) Should the investigator discover that one treatment is of superior therapeutic merit, he or she is ethically obliged to offer that treatment; the current understanding of this requirement, which entails that the investigator have no "treatment preference" throughout the course of the trial, presents nearly insuperable obstacles to the ethical commencement or completion of a controlled trial and may also contribute to the termination of trials because of the failure to enroll enough patients; **2)** An alternative concept of equipoise is based on present or imminent controversy in the clinical community over the preferred treatment; according to this concept of "clinical equipoise," the requirement is satisfied if there is genuine uncertainty within the expert medical community—not necessarily on the part of the individual investigator—about the preferred treatment.[11]

Error – **1)** A false or mistaken result obtained in a study or experiment; **NOTE:** Several kinds of error can occur in epidemiology, for example, due to bias[10]; **2) Random error (sampling error)** is that due to chance, when the result obtained in the sample differs from the result that would be obtained if the entire population ("universe") were studied; **NOTES:** a) Two varieties of sampling error are **Type I**, or alpha error, and **Type II**, or beta error. In an experiment, if the experimental procedure does not in reality have any effect, an apparent difference between experimental and control groups may nevertheless be observed by chance, a phenomenon known as Type I error. Another possibility is that the treatment is effective but by chance the difference is not detected on statistical analysis—Type II error[10]; b) In the theory of testing hypotheses, rejecting a null hypothesis when it is actually true is called **Type I error**; accepting a null hypothesis when it is incorrect is called **Type II error; 3) Systematic error** is that due to factors other than chance, such as faulty measuring instruments; **NOTE:** It is further considered in **Bias**.[10]

Health services research – The multidisciplinary field of scientific investigation that studies how social factors, financing systems, organizational structures and processes, health technologies, and personal behaviors affect access to health care, the quality and cost of health care, and ultimately our health and well-being; **NOTE:** Its research domains are individuals, families, organizations, institutions, communities, and populations.[9]

Hypothesis – **1)** In a trial, a statement relating to the possible different effect of the interventions on an outcome; **NOTE:** The null hypothesis of no such effect is amenable to explicit statistical evaluation by a hypothesis test, which generates a P-value[8]; **2)** A supposition, arrived at from observation or reflection, that leads to refutable predictions; **NOTE:** See also **null hypothesis**.[10]

Incidence – An expression of the rate at which a certain event occurs, for example, the number of new cases of a specific disease occurring during a specific period; **NOTES:** a) The number of instances of illness or other outcome commencing, or of persons falling ill, during a given period in a specified population; b) More generally, the number of new events, e.g., new cases of a disease in a defined population, within a specified period of time.[7]

Indirect cost – A cost which cannot be identified directly with a particular activity, service, or product of the entity incurring the cost; **NOTE:** Indirect costs are usually apportioned among an entity's services in proportion to each service's share of direct costs.[9]

Institutional review board (IRB) – In the U.S., the standing committee in a medical school, hospital, or other healthcare facility that is charged with ensuring the safety and well-being of human subjects involved in research; **NOTES:** a) The IRB is responsible for ethical review of research proposals; b) Many synonyms are used in other countries, e.g., *Ethical Review Committee, Research Ethics Board*; c) All research, including epidemiological research, that involves human subjects must be approved by an institutional review board or equivalent body.[7]

Intention-to-treat analysis – A strategy for analyzing data in which all participants are included in the group to which they were assigned, whether or not they completed the intervention given to the group; **NOTE:** Intention-to-treat analysis prevents bias caused by the loss of participants, which may disrupt the baseline equivalence established by random assignment and which may reflect nonadherence to the protocol.[8]

Justice – The duty to treat all fairly, distributing the risks and benefits equably; **NOTES:** a) The principle of justice requires that the benefits and burdens of research be distributed fairly; b) Vulnerable populations should not be targeted for research if other populations are also suitable; vulnerable populations and other populations, such as women, children, elderly, and minorities should be offered participation in clinical trials to ensure access to new, beneficial, or potentially lifesaving treatments.[6]

Matching – The process of making a study group and a comparison group comparable with respect to extraneous factors; **NOTE:** Several kinds of matching can be distinguished: (1) *Caliper matching* is the process of matching comparison group subjects to study group subjects within a specified distance for a continuous variable (e.g., matching age to within two years); (2) *Frequency matching* requires that the frequency distributions of the matched variables be similar in study and comparison groups;[7] (3) *Category matching* is the process of matching study and control group subjects in broad classes, such as relatively wide age ranges or occupational groups; (4) *Individual matching* relies on identifying individual subjects for comparison, each resembling a study subject on the matched variable(s); (5) *Pair matching* is individual matching in which study and comparison subjects are paired.[7]

Meta-analysis – **1)** A statistical synthesis of the data from separate but similar (i.e., comparable) studies, leading to a quantitative summary of the pooled results; **2)** *In the biomedical sciences*, the systematic, organized, and structured evaluation of a problem of interest, using information (commonly in the form of statistical tables or other data) from a number of independent studies of the problem; **NOTES:** a) A frequent application has been the pooling of results from a set of randomized controlled trials, none in itself necessarily powerful enough to demonstrate statistically significant differences, but in aggregate capable of so doing; b) Meta-analysis has a qualitative component, i.e., application of predetermined criteria of quality (e.g., completeness of data, absence of biases), and a quantitative component, i.e., integration of the numerical information. The aim is to integrate the findings, pool the data, and identify the overall trend of results; c) An essential prerequisite is that the studies must stand up to critical appraisal, and allowance must be made for various biases (e.g., publication bias);[7] **3)** A statistical procedure to combine results from different studies on a similar topic; **NOTES:** a) The combination of results from multiple studies may produce a stronger conclusion than can be provided by any singular study; b) Meta-analysis is generally most appropriate when there are not definitive studies on a topic and nondefinitive studies are in some disagreement.[9]

Multiple comparisons – The performance of multiple analyses on the same data; **NOTE:** Multiple statistical comparisons increase the probability of making a Type I error (i.e., attributing a difference to an intervention when chance is the more likely explanation).[8]

Nonmaleficence – The duty to cause no harm; **NOTE:** The principle of nonmaleficence requires that research design be scientifically sound and that the risks of the research be acceptable in relation to the likely benefits.[6]

Null hypothesis – **1)** In simplest terms, the null hypothesis states that the results observed in a study, experiment, or test are no different from what might have occurred as a result of the operation of chance alone; **2)** The hypothesis that the independent variable(s) under study has no association with or effect upon the dependent or outcome variable(s).[10]

Objectives – The general questions the trial was designed to answer; **NOTE:** Objectives may be associated with one or more hypotheses that, when tested, will help answer the question.[8]

Odds – The ratio of the probability of occurrence of an event to that of nonoccurrence, or the ratio of the probability that something is so, to the probability that it is not so.[10]

Odds ratio – The ratio of two odds[7]; **NOTES:** a) In a case-control study, the exposure odds ratio is the ratio of the odds of an exposure in the cases to the odds of an exposure in the controls; b) With incident cases, unbiased subject selection, and a "rare" disease (e.g., under 2% cumulative incidence rate over the study period) the exposure odds ratio is an approximate estimate of the risk ratio. [10]

Outcome –The results of the use of an intervention, a process, or medical care, the consequences of using a medical care process, or the consequences to the health and welfare of individuals or populations in a society; **NOTE:** Commonly used measures include: morbidity, mortality, quality of life measures, satisfaction with care, cost of care, length of stay, work days lost, complication rate, and readmission rate.

P (probability), P value – The letter P, followed by the abbreviation n.s. (not significant) or by the symbol < (less than) and a decimal notation such as 0.01, 0.05, is a statement of the probability that the difference observed could have occurred by chance, if the groups are really alike (i.e., under the null hypothesis); **NOTES:** a) Investigators may arbitrarily set their own significance levels, but in most biomedical and epidemiological work, a study result whose probability value is less than 5% ($P<0.05$) or 1% ($P<0.01$) is considered sufficiently unlikely to have occurred by chance to justify the designation "statistically significant;" b) See also **statistical significance**.[10]

Patient outcomes – The impact of medical care on a patient's well-being in terms that are perceptible to the patient; these include such things as functional status, health status, and quality of life.

Power//statistical power – **1)** The ability of a study to demonstrate an association if one exists; **NOTES:** a) The power of a study is determined by several factors, including the frequency of the condition under study, the magnitude of the effect, the study design, and sample size; b) Mathematically, power is 1-β (Type II error); **2)** A characteristic of a statistical hypothesis test, denoting the probability that the null hypothesis will be rejected if it is indeed false[7]; **3)** The probability that a trial will detect, as statistically significant, an intervention effect of a specified size; **NOTE:** The prespecified trial size is often chosen to give the trial the desired power.[8]

Prevalence – The extent of occurrence expressed as a fraction of the numbers affected by the disease or condition compared to the total number of members in the specified group; **NOTES:** a) When used without qualification, the term usually refers to the situation at a specified point in time (point prevalence); b) This is a number, not a rate.[7]

Quality-adjusted life years (QALY) – An outcome measure that incorporates the quality or desirability of a health state with the duration of survival; **NOTE:** The quality of life is integrated with the length of life by using a multiplicative formula.[12]

Randomization – In a randomized trial, the process of assigning participants to groups such that each participant has a known and usually an equal chance of being assigned to a given group; **NOTE:** Randomization is intended to ensure that the group assignment cannot be predicted.[8]

Randomized blinded trial – An experimental study design in which study subjects are allocated at random to interventions and study subjects are not aware of the intervention to which they have been allocated; additionally, study investigators or study personnel making outcomes measurements may also be unaware of the intervention to which study subjects have been allocated; **NOTE:** Random allocation controls confounding by known and unknown factors and blinding controls bias in study subjects reporting, study personnel measurements of outcomes, and investigators' analysis of study findings.

Reimbursement – The process by which healthcare providers receive payment for their services; **NOTE:** Because of the nature of the healthcare environment, providers are often reimbursed by third parties who insure and represent patients.[9]

Relative risk – **1)** Ratio of the risk (i.e., the probability or rate of occurrence) of an outcome in exposed vs. unexposed groups, synonymous with risk ratio (RR);[7] **2)** Alternatively, the ratio of the cumulative incidence rate in the exposed to the cumulative incidence rate in the unexposed, synonymous with rate ratio[7]; **NOTES:** a) The term relative risk has also been used synonymously with odds ratio (q.v.) and, in some biostatistical articles, has been used for the ratio of measures of the occurrence of death or other outcomes, often termed the forces of morbidity by epidemiologists and demographers; b) The use of the term relative risk for several different quantities arises from the fact that for "rare" diseases (e.g., most cancers with incidence rates measured as cases per 10,000 or 100,000), all the quantities approximate one another; for common occurrences (e.g., neonatal mortality in infants under 1500 g birth weight), the approximations do not hold;[7] **3)** The rate of disease in one group exposed to a particular factor divided by the rate in another group which is not exposed; **NOTE:** A relative risk of one indicates that the two groups have the same rate of disease.[9]

Sample size – **1)** The number of participants in the trial; **2) *Intended* sample size** – the number of participants planned to be included in the trial, usually determined using a statistical power calculation; **NOTE:** The sample size should be adequate to provide a high probability of detecting as significant an effect size of a given magnitude if such an effect actually exists; **3) *Achieved* sample size** – the number of participants enrolled, treated, or analyzed in the study.[8]

Statistical significance – Statistical methods allow an estimate to be made of the probability of the observed or greater degree of association between independent and dependent variables under the null hypothesis; from this estimate, in a sample of given size, the statistical significance of a result can be stated; **NOTE:** Usually the level of statistical significance is stated by the P value.[10]

Stratification – The process of or result of separating a sample into several subsamples according to specified criteria, such as age groups, socioeconomic status, etc.; **NOTES:** a) Stratifying the analysis of results may control the effect of confounding variables. For example, lung cancer is known to be associated with smoking. To examine the possible association between urban atmospheric pollution and lung cancer, controlling for smoking, the population may be divided into strata according to smoking status. The association between air pollution and cancer can then be appraised separately within each stratum; b) Stratification is used not only to control for confounding effects but also as a way of detecting modifying effects. In this example, stratification makes it possible to examine the effect of smoking on the association between atmospheric pollution and lung cancer.[7]

Subgroup analysis – An analysis in which the intervention effect is evaluated in a defined subset of the participants in the trial, or in complementary subsets, such as by sex or in age categories; **NOTE:** Sample sizes in subgroup analyses are often small and subgroup analyses therefore usually lack statistical power; they are also subject to the multiple comparisons problem.[8]

Survey – An investigation in which information is systematically collected; **NOTES:** a) A population survey may be conducted by face-to-face inquiry, by self-completed questionnaires, by telephone, by postal service, or in some other way; each method has its advantages and disadvantages; b) The generalizability of results depends upon the extent to which those surveyed are representative of the entire population.[9]

Systematic review – A systematic review is a concise summary of the best available evidence that addresses sharply defined clinical questions; **NOTES:** a) Systematic reviews differ from other reviews, often termed narrative reviews in several ways; systematic reviews address a focused clinical question, use an explicit search strategy applied to comprehensive sources, uniformly apply criteria for the selection

of sources, use rigorous critical appraisal to make evidence-based inferences; b) Systematic reviews that use quantitative methods to summarize evidence are termed "meta-analyses."[13]

Target population – The group of persons about whom an investigator intends to make inferences about the validity of study findings; **NOTE:** The target population may consist of all persons residing in a geographic area, persons with specific demographic characteristics, clinical characteristics, persons who receive services at specific source, or who have specific arrangements for financing or organization of care.

Type I error – An incorrect judgment or conclusion that occurs when an association is found between variables where, in fact, no association exists; **NOTES:** a) For example, if the experimental procedure does not really have any effect, chance or random error may cause the researcher to conclude that the experimental procedure did have an effect[9]; b) Also known as "false positive" or "alpha error"; c) See **Error**.

Type II error – An incorrect judgment or conclusion that occurs when no association is found between variables where, in fact, an association does exist; **NOTES:** a) In a medical screening, for example, a negative test result may occur by chance in a subject who possesses the attribute for which the test is conducted[9]; b) Also known as "false negative" or "beta error"; c) See **Error**.

Validity//study validity – The degree to which the inference drawn from a study is warranted when account is taken of the study methods, the representativeness of the study sample, and the nature of the population from which it is drawn; **NOTE:** Two varieties of study validity are distinguished: (1) *Internal validity*: The index and comparison groups are selected in such a manner that the observed differences between them on the dependent variables under study may, apart from sampling error, be attributed only to the hypothesized effect under investigation; (2) *External validity (generalizability)*: A study is externally valid, or generalizable, if it can produce unbiased inferences regarding a target population (beyond the subjects in the study). This aspect of validity is only meaningful with regard to a specified external target population. For example, the results of a study conducted using only white male subjects might or might not be generalizable to all human males, or to human females. The evaluation of generalizability usually involves much more subject-matter judgment than internal validity.[7]

Within-group design – A study design in which comparisons are made within a group of study subjects at two or more time periods during which the study subjects may have different environmental exposures, clinical treatments, or use of health services; **NOTES:** a) In observational studies, comparisons are made between two time periods when study subjects have different exposures, treatments, or use different health services; b) Observational within-group designs are used when it is not feasible or ethically permissible to control the exposures, treatments, or use of health services; c) In experimental studies, comparisons are made between two or more time periods when study subjects have been allocated, ideally at random, to different clinical treatments or the use of specific health services; d) Within-group designs have an advantage in that fewer study subjects are needed and study subjects can serve as their own controls; e) Within-group designs have the disadvantages that they may take longer to complete and are subject to potential bias due to patient conditions that may change over time, carry-over effects from previous interventions, or secular changes in the healthcare system.

4 Outcomes Studies and Health Services Research

Scientific research is a systematic activity that is designed to answer questions and test hypotheses about the universe. Outcomes studies are a subset of a broad field of research called "health services research." Health services research examines the use, costs, quality, accessibility, delivery, organization, financing, and outcomes of healthcare services to increase knowledge and understanding of the structure, processes, and effects of health services for individuals and populations.[14] Outcomes studies are directed toward the end results of healthcare services, the effect of the healthcare service on the health and well-being of

individuals and populations. Outcomes research focuses on the use of health services, the effectiveness of health services on patients' health, health-related quality of life, satisfaction with care, and resources and costs of health services to achieve these outcomes. Such studies often provide the evidence needed to translate basic research into practice. Thus, well-designed outcomes research assists with quality improvement, technology assessment, patient safety, policy development and implementation, and practices to improve patient outcomes, reduce errors, and control costs.

4.1 Essential Features of Outcomes Studies

Broad Range of Factors: The World Health Organization (WHO) has endorsed a broad definition of health as, "a state of complete physical, mental, and emotional well-being and not merely the absence of disease or infirmity." Outcomes studies can provide new ways of examining and understanding health and the many factors that influence health, including those associated with the occurrence of disease and illness, structure of the healthcare system, and process of providing healthcare services. Outcomes studies address a broad range of factors including human biology, science and technology (drugs, devices, and procedures), personal factors including health-related behavior, family and community factors, and characteristics of the healthcare system. Outcomes studies address a wide variety of settings (home, physician's office, health clinic, emergency department, hospital, and long-term care settings).

Broad Range of Outcomes: Outcomes studies address a broad range of outcomes that are affected by health and health care. Patient outcomes can be classified into four domains:

- Clinical and functional outcomes. These include the occurrence and status of diseases, injuries, and conditions and their impact on physical and mental health. These outcomes include symptoms and signs of disease; results of laboratory tests to assess health status (laboratory tests, imaging tests, and other tests of organ physiology); and functional measures, such as activities of daily living (eating, toileting, dressing, bathing, transferring from bed to chair, and walking).

- Health-related quality of life. These inherently subjective outcomes include self-reported judgments of a person's physical function, mobility, mental functioning, social function, and role functioning. Health-related quality of life outcomes include generic measures of outcomes that apply to all persons and disease- or condition-specific measures that apply to persons with a specific disease or condition. Disease- or condition-specific measures may be more sensitive to interventions for these diseases or conditions than generic outcomes measures.

- Preferences for health. Patients' preferences, values, and satisfaction with their health status are important outcomes measures that influence their health-related behaviors, illness experience, use of healthcare services, and adherence to treatment programs and lifestyle modification. Methods are available to assess patient preferences, and these outcomes are increasingly included in outcomes research.

- Resource use and costs. The use of resources in health care and the costs of healthcare services are important outcomes. The aging of the population; development of new and expensive drugs, devices, and technologies; and increased demand for health services in the United States have increased healthcare costs. The mix of public and private programs for organization and financing of healthcare services and the competing priorities for public and private funds for healthcare services have heightened the interest in resource use and costs as outcomes measures in outcomes research.

Practical and Pragmatic: Outcomes studies are often pragmatic compromises between the ideal study and no study at all. Every study has some constraints placed on it. In some studies, limiting constraints may be limited money, research staff, or time to perform the study. For example, a decision may need to be made by a certain time about the purchase of another blood gas instrument. In other circumstances, human subjects' safety considerations may place restrictions on when or how a study can be conducted.

An investigator should explore carefully whether any existing data (from computerized records, previously conducted patient satisfaction surveys, or the literature) might be used to conduct the study before embarking on new or additional data collection. In many cases, investigators may find that their institution already has data or information that could be used to study patient outcomes. The ability to recognize when these "natural" experiments are possible requires an understanding of the basic elements of outcomes studies that are outlined below. Each patient outcomes research study may therefore require a different pragmatic compromise in the perspective, resources, and time needed to address the research question. Patient outcomes research, as all research, produces incremental knowledge—rarely is any single study a definitive study. For all interested parties and stakeholders to be confident that the findings are valid and generalizable, patient outcomes research studies need to be replicated in different settings for a diverse range of patients.

Outcomes Studies are Interdisciplinary and Conducted by Teams of Investigators: Outcomes studies are often interdisciplinary in nature. Individuals who have been trained in a laboratory science or in a clinical specialty may not have sufficient expertise to investigate the required relationship between a laboratory test and a clinical outcome. However, they could work together to conduct a study that could advance the whole healthcare field. Investigators are encouraged to seek input from many disciplines to ensure the greatest benefits using the best science. A team of investigators with expertise in a variety of clinical, managerial, and research disciplines is usually assembled by a lead or principal investigator to carry out a patient outcomes research study.

Outcomes Studies are Research: Patient outcomes research is conducted to answer questions and test hypotheses about the use of health services and their effect on patients—an important theme of broad interest to patients, providers, healthcare managers, and insurers. Patient outcomes studies should follow the principles as described in this guideline. Investigators who conduct patient outcomes research should publish and disseminate their findings. This distinguishes outcomes research from quality assurance activities, quality improvement programs, and other tasks of those who manage health services.

4.2 Setting Priorities for Outcomes Research

Outcomes research may be conducted by investigators in different organizations such as universities, academic medical centers, foundations, research organizations, and community hospitals. Investigators working in these organizations will often be interested in different aspects of a health services research issue, and organizational priorities in selecting outcomes research studies may differ. Government agencies, healthcare providers, insurers, and others each have a set of priorities based on their own specific agendas. In the planning for patient outcomes research, investigators may find it useful to consider the following six factors in setting priorities for patient outcomes research projects:

- The burden of disease. This can be described by several measures, such as the occurrence of new cases of disease in a population during a specific time period (incidence); the proportion of patients with a disease or condition (prevalence); the duration of time individuals are affected by a disease (clinical course of disease); the premature loss of life to a disease (years of potential life lost or YPLL); or other related measures. The type of measure of burden of disease may vary depending upon the setting (community, hospital, nursing home); the patient population (persons living in the geographic area, persons insured by a specific insurance company, employees of a specific company, persons using a specific facility, etc.); the nature of the diseases; and the time frame for the research. Measures of burden of disease may also indicate the severity of disease or the impact of the disease, such as measures of restricted activity, work-loss days, school-loss days, or bed-days. Finally, the measure of the impact of the disease on patients' quality of life can be combined with the duration of time the patient experiences a reduced quality of life to produce a quality-adjusted life year or QALY.

- Gaps in knowledge or variations in the processes of care or outcomes of care. Variations occur in all measurements in the biological and clinical world, and variation occurs as well in measurements of

the use of health services and patient outcomes. Variations that are strikingly large and apparently unexplained by readily available data and observations should be interpreted as indicators of potentially important areas for further investigation. Variations may also reflect unmeasured factors, such as comorbid conditions, patient lifestyle factors, patient preferences regarding the use of health services, or physician practice style. Variations are important for patient outcomes research, because they may indicate uncertainty about best practices, need for further research to evaluate the role of patient preferences, and other factors in processes of care. Variations may also indicate opportunities for quality improvement programs.

- Finding ways to reduce the cost of care. Healthcare costs are one important component of patient outcomes research. The increase in healthcare costs may be the reason for a patient outcomes study or the main focus for the study. Healthcare costs accrue from the use of resources as well as the impact of the illness on patients, patients' families, employers, and the community. The measurement of healthcare costs is complex, and the study team should include investigators with expertise in finance and health economics to address these issues.

- Government needs. Governments are the single-largest payers of healthcare services and are vitally interested in whether these resources are achieving good patient outcomes. An important consideration in setting priorities for patient outcomes research is the funding available for such studies. Government agencies indicate their priorities partly by making funds available through research grants and contracts and are major sources of support for patient outcomes research.

- Community, institutional, and local needs. Patient outcomes research should be planned with an understanding of the conditions and diseases that are prevalent, morbid, or of particular concern to the local community. The conditions and diseases, illnesses, and questions that are important to providers and managers of clinics, hospitals, and other institutions that provide care will often determine whether patient outcomes studies are performed in these settings.

- Sources of funding. "What gets funded gets done," the saying goes. Patient outcomes research requires the participation of patients and their families, the cooperation of the patients' healthcare providers and other clinicians, and expertise of a research team. Patient outcomes research takes time to plan, implement, analyze, interpret, and disseminate. The research personnel, space, equipment, and supplies must be supported. Thus, research funding from federal and state governments, foundations, private organizations, and local institutions is an important consideration in the design and planning of patient outcomes research.

4.3 The Cycle of Outcomes Research

Outcomes research often begins from an observation of current practices and a desire to improve outcomes, reduce adverse outcomes, or reduce costs (see Figure 1).

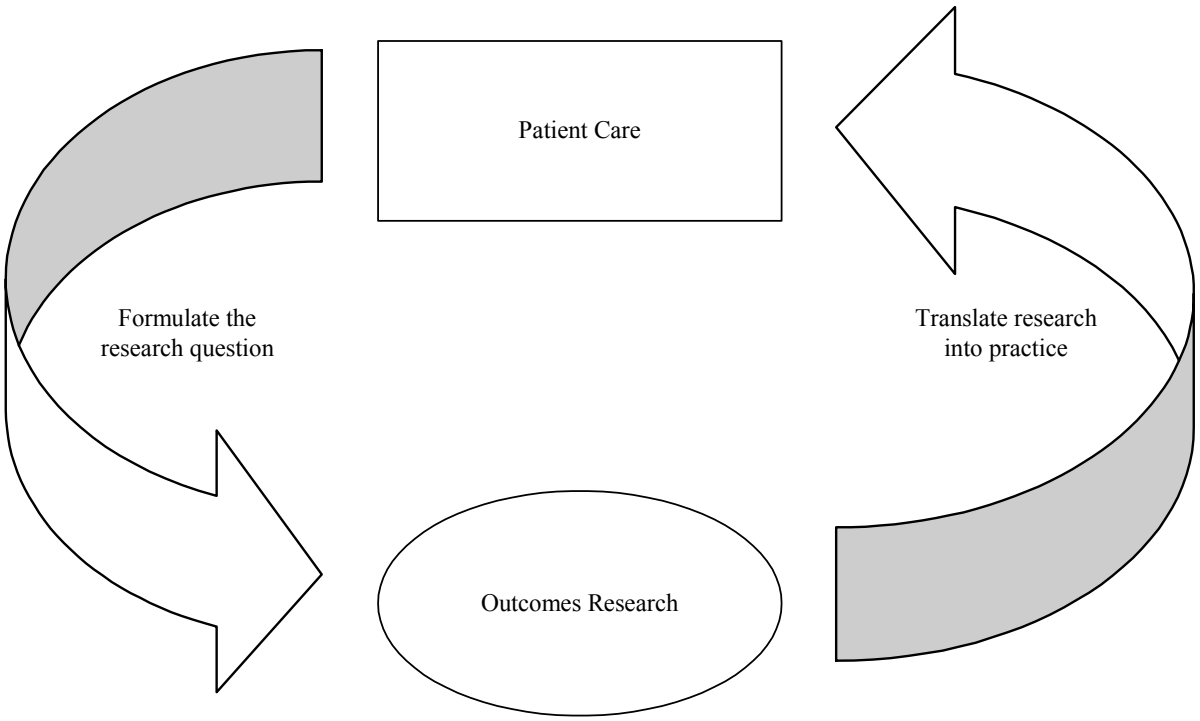

Figure 1. Patient Care and Outcomes Research

First, the investigator identifies the specific healthcare service to be studied, the persons (patients) to receive the services or be affected by the services, the interventions to be tested, and the outcomes to be measured. At this stage an investigator will state one or more questions to be answered and develop a plan for a study to address these questions. The investigator may have several ideas about factors associated with health outcomes or plans to test an intervention that may improve health outcomes. The investigator will consult with others who have experience in conducting research or similar studies in this area; consult with colleagues who have expertise in specific tests, treatments, and therapies; and review the scientific literature to learn whether the ideas have been previously studied and what is known about their effectiveness. The investigator searches for information about institutional, organizational, regional, or national issues that are relevant to the health outcomes or might influence, assist, or hinder a study of outcomes. At this point, the investigator designs a study to answer the study questions, measure specific outcomes, and test specific interventions in a specific setting. The investigator then drafts a study protocol, assembles a team of investigators, identifies resources and funding necessary to conduct the study, and addresses ethical issues. The draft will be revised into an explicit, detailed proposal, which describes the study proposal, investigators, resources, timeline, and budget. The study will be submitted to the institutional committees for review and to the institutional review board (IRB) or ethics committee for human studies. The research plan may be revised in response to review by persons or organizations with expertise in research methods, the clinical care of patients, or management of tests, technologies, or services to be studied. A small feasibility or "pilot" study may be conducted to clarify procedures to recruit patients, implement study interventions, and provide initial data for sample size estimates. Finally, the study will be approved and implemented. Eligible patients will be enrolled, baseline measurement taken, one or more interventions implemented, and outcomes recorded. The results of the study will be analyzed and decisions made about whether or not the results support the intervention. If the intervention is supported, a decision may be made to adopt the change. Regardless of the outcome, the investigator should submit the study results to peer-reviewed journals. The study will be accepted for publication (after suitable revisions are made) and published. The study findings may be reported in the lay literature. The study will be disseminated to other settings and used by others to improve patient care (see Figure 1),

and possibly modify local, state, regional, or national health policies. The steps in this cycle are shown in Table 1.

Table 1. Steps in Outcomes Research

Planning the Study
• Formulate the research question • Assess feasibility • Assess scientific merits • Review literature • Assess relevance to practice • Develop specific aims & hypotheses • Select study design • Choose study setting and sites • Develop criteria for subject eligibility & exclusion • Plan analysis & sample size • Assess threats to validity (chance, bias, confounding) • Assess human subjects & ethical issues • Write protocol • Submit to institutional review committees • Obtain administrative approval • Secure funding
Conducting the Study
• Assemble team • Train staff • Establish procedures & operations • Recruit subjects • Measure baseline characteristics • Apply intervention, if an interventional study design • Measure outcomes • Analyze results • Assess chance, bias, & confounding • Interpret findings
Reporting & Disseminating the Study
• Submit for publication • Report results to institution and funding agencies • Translate research into practice

This cycle of outcomes research requires enthusiasm, patience, resources, and time. It is enormously important in its potential to improve the processes of health care and health outcomes. Patients and their families, healthcare providers, healthcare managers, payers, and policy makers all have a stake in assuring that outcomes research is of the highest possible quality to provide valid and generalizable knowledge with the most efficient use of limited resources available for outcomes research.

5 Planning Patient Outcomes Research

The following sections provide general information about essential factors that healthcare providers, managers, and other potential investigators should consider when planning to conduct or evaluate patient outcomes studies. It will be useful for investigators to separately consider the *components* of outcomes research represented in the written outcomes research proposal and *process* of outcomes research or the outcomes research workflow (see Figure 2).

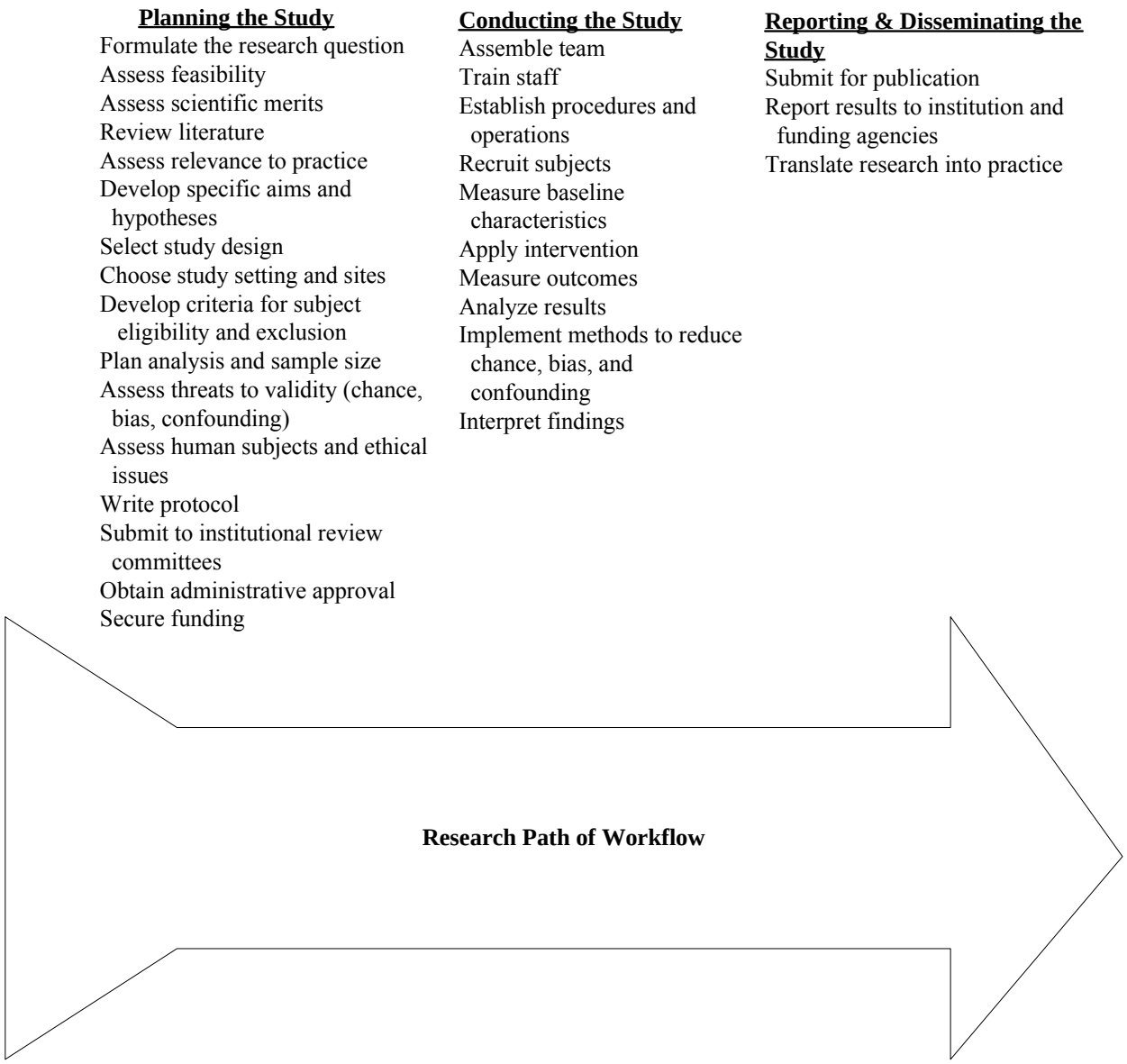

Figure 2. Outcomes Research Path of Workflow

5.1 Resources for Planning Outcomes Research

Investigators planning to conduct outcomes research should seek assistance from colleagues with experience in conducting clinical and outcomes research. Valuable assistance in design, implementation, analysis, and reporting of outcomes research may be available from faculty in academic medical centers, universities, schools of public health, staff of professional organizations, foundations, and government agencies that conduct research and provide funds for research. Collaboration with experienced investigators may be an efficient way to develop an outcomes research program. Information on outcomes research is available from many books, monographs, journals, and the World Wide Web (see the Additional References section).

5.2 Formulating the Research Question

Of fundamental importance in conducting or evaluating outcomes studies are some very practical questions. First, what is the health service that is the focus of the study? What are the specific interventions to be studied and what are the alternatives to be investigated? Second, who will experience the improved outcomes? Third, what are the outcomes and can they be measured? The study may focus on a service to see if it is actually effective in improving outcomes, how well it works, or how much it costs.

5.2.1 Study Goals, Specific Aims, and Hypotheses

One of the most critical aspects of conducting any study is ensuring that the research question(s) are aimed at a measurable, appropriate, and meaningful outcome. The goals of the healthcare organization; physicians and other healthcare providers, insurers, and payers; the patients receiving healthcare services; and the persons residing in the community may differ. The overall goals and aims of the research program should be described clearly to everyone involved to attain success. One of the best ways to achieve success is to craft a series of questions around the issue to be studied and then prioritize them. Each of the study questions should be recast as a specific aim of the study. For each relevant and supported question that is developed into a specific aim, a working hypothesis is developed. In outcomes research, the investigators may have a "conceptual framework" that describes the hypothesized relationship between one or more clinical factors, health behaviors, health services, or other factors and the health outcomes. In biomedical and clinical research, the focus of the specific aim may be on establishing the likelihood of the truth of the hypothesis. In outcomes research and health services research, the focus of the specific aim may be on estimating the magnitude of an effect of some factor on an outcome such as the amount of improvement in health status, function, survival time, or cost savings rather than simply testing the hypothesis to observe some change in an outcome. The most important aim should be selected as the primary study aim and the other study aims, while interesting and important, should be listed as secondary aims. The primary aim will determine the overall study design, interventions, outcome measurements, and follow-up of study subjects. Thus, the primary aim of the study will determine the size of the study, resources required, and duration of the study.

5.2.2 Testing Hypotheses

Statistical theory provides a framework for testing hypotheses and estimating the magnitude of effects of factors on outcomes. The investigator's judgment about the likely relationship of factors of interest on outcomes is explicitly stated as a hypothesis. Hypotheses cannot be directly proved. It is possible, however, to state null hypotheses, asserting that there is no relationship between an effect on an outcome or that the magnitude of the effect on an outcome is smaller than a certain magnitude. Statistical theory allows the calculation of the probability (a "P-value") that the findings in the study occurred by chance. If the probability of the results occurring by chance is small (e.g., less than 5% or 1%), then the investigator rejects the null hypothesis as unlikely, and based on the evidence in the study, concludes that the study hypothesis is true (or at least more likely to be true than believed prior to performing the study).

5.2.3 Estimating the Magnitude of Effects of Factors on Outcomes

In outcomes research, hypotheses often include judgments about the magnitude of an effect. This is often selected based on a physician's or provider's estimate of the expected outcomes. In addition to testing hypotheses that outcomes are at least a certain magnitude in size, statistical theory also provides calculation of a range or interval that is likely to include the true magnitude of effect, based on the results of the study. This range may be expressed as a confidence interval; most often, a 95% confidence interval is reported.

5.2.4 Errors in Inference

There is a natural analogy to interpretation of diagnostic tests, like laboratory tests, and interpretation of scientific hypotheses. Hypotheses may be true or false. An investigator's judgment about the truth of a hypothesis may be correct or may be an error. If the research hypothesis is true, and the investigator concludes that the hypothesis is true, or if the research hypothesis is false and the investigator concludes that the hypothesis is false, then there is no error.

Two types of error may occur, analogous to a false-positive and a false-negative diagnostic test. The research hypothesis may be false, but the statistical analysis of the study data results in a small P-value, and the investigator rejects the null hypothesis and falsely concludes that the research hypothesis is true. This is a false-positive conclusion and is described by statisticians as a T*ype I error* or *alpha error*.

The research hypothesis may be true, but the statistical analysis of the outcomes study results may have resulted in a P-value that was large, and accordingly the investigator could not reject the null hypothesis and falsely concludes that the research hypothesis was not likely. This is a false-negative conclusion, described by statisticians as a *Type II error, beta error*, or *power*.

5.3 Validity, Sources of Error, and Strategies to Reduce Error

A study has *internal validity* when the study's conclusions are true (i.e., the study findings about the relationship between the factors of interest and the outcomes describe the real relationship between these factors and the outcomes in the patients actually enrolled in the study). A study has *external validity* when inferences about the relationship between the study factors of interest and the outcomes describe the real relationship between these factors and the outcomes of interest in patients similar to those enrolled in the study—the target population. A study may have internal validity but lack external validity, because the study subjects enrolled in the study are not representative of the target population, and the relationship between the factors of interest and the outcomes in the enrolled study subjects do not reflect the relationship between the factors of interest and the outcomes in the target population.

Chance, bias, and confounding are the three major sources of error in patient outcomes research. Investigators should anticipate potential sources of error and plan the study to minimize the role of error in the design and implementation of an outcomes research study. While it is impossible to eliminate all sources of error, investigators should understand the potential sources of error in outcomes research and should anticipate and plan for error reduction at design, implementation, and analysis stages of outcomes research.

- *Chance* describes the effect of random events (bad luck). Chance should be anticipated, and efforts should be made to reduce the role of chance (random error) in the design of the study and the analysis of outcomes research. Statistical theory provides powerful methods for understanding random variation as sources of errors, describing variation, testing hypotheses, and estimating magnitude of outcomes in the presence of random error. Ensuring an adequate sample size and replicating measurements may reduce error due to chance. Sample size should be estimated using information from preliminary studies, published literature, other investigators, and expert opinion.

- In epidemiology and in patient outcomes research, *bias* describes systematic errors due to sampling of persons, types of measures, or measurements. Bias can occur in the selection of study subjects, baseline measurements, implementation of interventions, follow-up of study subjects, or assessment of outcomes. Bias can be reduced by anticipating potential sources of bias in sampling study subjects, selecting measurements, and making measurements. Bias may be reduced by blinding study subjects, healthcare providers, and study personnel to study aims, interventions, measurements, and analysis. Bias can also be reduced by standardizing as many aspects of the intervention or study protocol as are under the control of the investigator. Bias can be controlled in the design of a study. Bias can be

suspected in analysis of information obtained in the study, but cannot be eliminated in analysis. The investigator should assess the potential role of bias by obtaining information on the target population, the eligible population, and the characteristics of the study subjects in each of the intervention groups to identify factors associated with allocation to intervention groups. Finally, the pattern of dropouts and any losses to follow up in each of the intervention groups should be assessed to determine how they might affect the study conclusions.

- *Confounding* is error that results from unmeasured, extraneous factors. Confounding can be controlled in design by anticipating as many potential sources of error as possible and obtaining measurements of these factors (e.g., severity of illness measures, case-mix). Potential confounders have been anticipated, and measures can be controlled in analysis by restriction, stratification, matching, or multivariable analyses. In clinical trials, unmeasured potential confounders can be controlled in interventions by random allocation of study subjects.

5.4 Assessing the Feasibility of the Study

Judgments of the scientific merits of the study are based on whether the research question is interesting, novel, and relevant. These judgments are influenced by current knowledge, gaps in knowledge, professional and scientific assessment of current state of the art, and institutional and organizational priorities. Outcomes research takes time and effort and may require substantial resources. The investigator should be interested, enthusiastic, and even passionate about the outcomes. It is difficult to sustain the effort and maintain the investigative team focus when the principal investigator and co-investigator are not fully committed to conducting the research and learning the results of the study. An outcomes research study could study a new service, a new outcome, a different population, or include new measurements. Before embarking on any study, it is important to determine whether anyone else has already explored the question or issue of interest. A review of the literature, looking for related studies and particularly for a meta-analysis of previously conducted studies, may provide the answers needed. However, the strengths and weaknesses of previous studies must be taken into account before deciding that no further evidence is needed beyond already existing information. Studies may be conducted to replicate findings elsewhere, especially if previous findings were unexpected or led to conclusions that are contrary to prevailing beliefs or understanding. If the study is being conducted primarily to confirm or replicate prior studies in a different setting, the investigators are encouraged to find ways to address new aspects of the study.[15]

Investigators can evaluate the potential relevance of research by considering the burden of disease, variations in process and outcomes of care, cost of care, federal and local government priorities, local institutional and community concerns, and availability of funding in the planning of outcomes research. Investigators should consider how strong the evidence of a difference in patient outcomes must be in order to persuade those involved in decision making about a need for a change in a practice or policy.

The following should be considered in assessing the feasibility of a planned patient outcomes study:

- scientific feasibility of the study (specific aims, hypotheses, study subjects, measurements, clinical important differences, detectable measures, adequate sample size);

- availability of study subjects (types and number);

- resources (space, equipment, supplies), expertise, time, money, personnel; and

- whether the scope of the study is manageable by the investigative team.

5.5 Addressing Ethical Issues

Patient outcomes research is human research, and investigators must consider issues related to the ethical conduct of studies with human subjects. The issues related to the conduct of the study are: (1) ethical principles that guide research with human subjects; (2) federal rules and regulations governing research with human subjects; (3) informed consent; (4) vulnerable populations requiring special protections; and (5) investigator responsibilities regarding scientific misconduct, conflicts of interest, and authorship.[6]

5.5.1 Ethical Principles and Patient Outcomes Research

The ethical principles that guide outcomes research and other studies with human subjects are *autonomy* (respect for persons), *beneficence* (promoting good outcomes), *nonmaleficence* (avoiding harm), and *justice*. The principle of autonomy is the basis for procedures to obtain informed consent, ensure the privacy of research subjects, ensure confidentiality of data, and protect the safety of vulnerable study subjects with impaired decision-making capability. Beneficence and nonmaleficence are the basis for procedures to ensure that the research is scientifically sound and that the risks to study subjects are reasonable in relation to the benefits. Justice requires that the benefits and burdens of research participants be distributed fairly to persons in the community.

In randomized trials where investigators assign study subjects randomly to interventions that may be beneficial or harmful, there should be a state of *equipoise*,[11] the judgment that current evidence does not clearly favor one intervention and that there is uncertainty about the best treatment.

5.5.2 Regulations and Laws Regarding Human Subjects Research

Investigators should be aware of all relevant government rules and policies regarding research, and the research should adhere to these rules, regulations, and applicable laws. Rules, regulations, laws, and policies for conducting research vary by country, region, local government, and individual organization and institution. Therefore, investigators are advised to check with their own institution and local research programs and seek advice from active and experienced investigators. In addition, investigators who accept samples from outside of their country may need to adhere to laws of the country from which the patient samples originated. For example, in the U.S., the Department of Health and Human Services has issued regulations governing human subjects research.[16] In addition, the Health Insurance Portability and Accountability Act (HIPAA)[17] applies to individually identifiable health information that has been electronically transmitted or maintained. All research protocols should be reviewed by the principal investigator's institutional review board (IRB) or ethics committee (EC) to determine the risk that human subjects will incur as a result of participation in the study. If the investigator's institution does not have an IRB or EC, the investigator should identify an IRB or EC to conduct a review of the research.

5.5.3 Informed Consent

Informed consent requires that investigators disclose all relevant information so potential study subjects can make an informed decision about participation in the study. Informed consent is a process to ensure that potential study subjects make informed decisions. A signed consent form indicates a willingness to participate in a study after there has been a thorough discussion between study subjects and the study investigator. Obtaining a subject's signature on a consent form itself does not ensure that the subject's decision has been an informed decision.

The components of informed consent are: (1) discussion of the nature of the research project; (2) the procedures of the study; (3) risks and benefits of participation and the alternatives to participation; (4) procedures to maintain confidentiality; and (5) assurance that participation is voluntary. The informed consent process is documented in a written consent form. Subjects who lack decision-making capability may participate in research if consent is obtained from the subjects' legally authorized representatives.

Research in vulnerable populations receives additional scrutiny to assure ethical conduct. Vulnerable populations include children, prisoners, pregnant women, fetuses, embryos, and persons with impaired decision-making capacity. Human subjects expect that they will be informed of the risks involved in their participation in a study. Patients have a right to expect that their personal or family information will be held in confidence and will not be known to others or released to others, without their consent.

Research protocols should be designed with the safety of everyone involved in the study in mind. The risk to healthcare personnel as well as patients needs to be considered, and any unnecessary risks should be avoided.

5.5.4 Investigator Responsibilities

Investigators who conduct outcomes research should adhere to the highest possible standards to ensure validity of research and to protect the safety of subjects. Investigators are responsible for research misconduct (fabrications, falsifications, and plagiarism)[18] and should also be careful to avoid conflicts of interest or the appearance of conflicts of interest.

Conflicts may occur when clinicians have roles as investigators. The physician's interest in advancing the outcomes research may influence management of patients, and patients' decisions to participate in research conducted by their physician may be influenced by their relationship. Financial conflicts of interest may occur when a funding source has an obvious interest in specific outcomes of a study, or when investigators, their departments or institutions, or their family members may benefit financially (or potentially lose opportunities for financial benefits) from particular results of a study.

Investigators also have ethical responsibilities for honesty in authorship of work submitted for publication. Outcomes research usually requires an interdisciplinary team of investigators and research staff. Authorship has responsibilities; authorship is merited when investigators have made substantial contributions to the conception, design, analysis, or interpretation of a study, and the writing and revisions of the manuscript. All authors must be willing to take responsibility for the research or for the portions under their control. At least one author must take responsibility for the entire research project. All authors must give final approval of manuscripts submitted for publication, and all authors must have access to the data. Participation in work to obtain funding and resources for the study, supervision of clinical or organizational sites where the study is conducted, data collection, administrative support of the research team, and preparation of the manuscript should be acknowledged but do not meet criteria for authorship.

5.6 Explicit Written Study Plan

All outcomes studies should be described in an explicit written study plan (see Table 2). There are several reasons to prepare a written study plan. First, the preparation of a study plan will clarify and improve the scientific basis of study (address important gaps in knowledge, avoid duplication, anticipate and minimize sources of error, use resources efficiently). Second, the written study plan will assist the investigators in assessing the feasibility of the study and obtaining funding and other resources for the study. Finally, the written study plan will assist the investigators, reviewers, and others in addressing human subjects issues (informed consent, privacy of study subjects, confidentiality of data, risks, benefits, and risks in relation to benefits) in the conduct of the study. Thus the written plan is important to the investigators, the institutions where the research will be performed, the funding organizations, the communities in which the study will be conducted, and the agencies and governmental bodies responsible for oversight of conduct of research to ensure the ethical conduct of the study.

The written study plan therefore contains information for assessing the scientific merits of the research, the feasibility of the research, resources needed to successfully complete the research, and the ethical issues in conduct of the research. The format and order of the components of the study plan will vary

depending upon the specific requirements of the institutions that are conducting the study, providing funds or other resources for the study, or reviewing the study to ensure ethical conduct and protection of human subjects. It is also important to define the roles and responsibilities of all investigators in the project and to obtain concurrence on these before the project is started. The study plan should include information on the study setting and how the study will be conducted. Ideally, the written plan would indicate manuscripts, reports, and other products of the study, and how the findings would be disseminated. The written study plan could also indicate how the study findings could be translated into practice.

Table 2. Components of a Study Plan

Study Plan
Title
Summary
Specific aims
Background
Preliminary data
Methods
Design
Study subjects
Measurements
Interventions and follow-up
Analysis, including sample size and power
Potential pitfalls and precautions taken
Human subjects and ethical issues
References
Investigators
Resources and research environment
Budget and timeline

6 Conducting Patient Outcomes Research

Investigators and other persons who are interested in planning, conducting, and using outcomes research should be familiar with the general features of the primary observational and interventional study designs. Primary research study designs (either observational studies or interventional studies) are the major focus for outcomes research. Investigators should also understand the role of the secondary (or integrative) study designs and their relationship to outcomes research.

6.1 Overview of Designs

Primary research designs collect new data or use existing data from individual study subjects and other sources to answer research questions about outcomes. There are two categories of primary research designs: (1) *observational research designs* collect information on study subjects and their health outcomes but are not designed to alter the structure of the healthcare system or the processes of care, and therefore the research study itself does not directly affect or alter health outcomes; (2) *interventional research designs* (or experiments) directly alter the structure of the healthcare system or the processes of care and collect information on the study subjects and their health outcomes. The strengths and limitations of observational and interventional study designs are summarized in Table 3.

Table 3. Observational and Interventional Studies

	Strengths	Limitations
Observational Studies	• May be used when intervention is not feasible or ethical • Surveys are rapid and efficient. • Case-control studies for rare events • Retrospective cohort and case-control studies may use existing data. • Surveys and retrospective cohort studies may be completed in less time than a prospective cohort study or a clinical trial. • Expenses are lower.	• Surveys do not permit true assessment of time sequence of factors and outcomes • Subject to bias and confounding • Limited power to study rare risk factors or rare outcomes in surveys and cohort studies
Interventional Studies	• Strong evidence for causation • Control selection of study subjects • Control quality of measurements • Multiple outcomes measurements	• More time; costly • Some interventions may not be feasible to control.

6.2 Observational Study Designs

The three major observational research study designs are *cross-sectional studies (surveys), cohort studies*, and *case-control studies*. The strengths and limitations of the three types of observational study designs are summarized in Table 4.

6.2.1 Cross-Sectional Study Design or Survey

A cross-sectional study design or survey is an observational study design that can be used in patient outcomes research to study the association of one or more factors with one or more outcomes. Information on one or more factors of interest (risk factors) is collected, and information on one or more outcomes of interest is also collected. The information on risk factors and outcomes may reflect information on the status of risk factors at the time the data are collected, or in a specific time interval, such as a week or month or other interval prior to the time of data collection.

6.2.2 Case-Control Study

A case-control study design is an observational study design that can be used to identify the relationship of one or more factors to an outcome. In a case-control study, persons who have experienced the outcome of interest ("cases") are identified, and persons who have not experienced the outcome ("controls") are selected. The presence of one or more patient, illness, or health system characteristics ("risk factors," "exposures," or "health services") in the cases is compared to the presence of these factors in the controls. The two important features of case-control study design are: (1) the selection of cases and controls; and (2) the assessment of the presence of factors of interest in the cases and controls.

The cases are selected based on the occurrence of an outcome. The "controls" or study subjects in the comparison group are selected from *all persons at risk of the outcome experienced by the cases* but who did not experience the outcomes. The assessment of the presence of factors of *interest prior to the time of occurrence of the outcomes in the cases* is made in *both the cases and controls*. The unique strengths (and limitations) of case-control studies are consequences of these features.

6.2.3 Cohort Study

A cohort study is an observational study design that can be used to study the relationship of one or more factors to more than one outcome. In a cohort study, a group of persons at risk for outcomes of interest is identified and followed over time. The presence of risk factors, exposures, or use of health services in

each of the study subjects at baseline, and possibly also during the course of the study, is ascertained. The study subjects are followed over time, and the occurrence of one or more new outcomes is ascertained. The incidence of new outcomes in study subjects with risk factors, exposures, or services of interest is compared to those without these factors. In a prospective cohort study, subjects are identified and followed for the occurrence of future outcomes. In a retrospective cohort study, subjects in the past at risk for an outcome are identified, and information collected from study subjects, medical records, or other sources is used to determine whether one or more outcomes have occurred. In retrospective cohort studies, although both the presence of risk factors and outcomes occurred in the past, the key feature is that an entire group of study subjects at risk for outcomes is identified, and the occurrence of the outcomes of interest in all persons at risk for the outcomes is ascertained.

Table 4. Observational Study Designs in Patient Outcomes Research: Cross-Sectional Surveys, Cohort Studies, and Case-Control Studies

Study Design	Strengths	Limitations
Cross-Sectional Studies	• Short duration • Control selections of subjects • Multiple risk factors • Multiple outcomes • Estimates prevalence, relative prevalence • First step in cohort study	• Subjective report of time sequence of factors and outcomes • Limited ability to assess causal associations • Potential bias in measuring predictors • Potential survivor bias • Not feasible for rare conditions • Does not yield incidence or true relative risk
Case-Control Studies	• Ideal for rare outcomes • Short duration • Relatively inexpensive • Relatively small sample size • Yields odds ratio	• Susceptible to bias in sample of two populations (cases and controls) • Potential bias in measuring predictors • Potential survivor bias • Limited to one outcome • Does not yield prevalence, incidence, or excess risk
Cohort Studies, in general	• Establishes time sequence • Avoid bias in predictors • Multiple outcomes • Number of events increases with time • Yields incidence, relative risk, and excess risk	• Large sample size • Not feasible for rare outcomes
Prospective Cohort Studies	• More control over selection of study subjects and measurements	• Longer duration and more expensive • Losses to follow up • Changes in criteria and methods over time
Retrospective Cohort Studies	• Shorter duration and less expensive	• Less control over selection of study subjects and over measurements

6.3 Interventional Designs

The two major interventional research designs are *randomized blinded trials* and *nonrandomized trials*. The strengths and limitations of randomized blinded trials and nonrandomized trials are summarized in Table 5.

6.3.1 Randomized Blinded Trial

A randomized blinded trial is a prospective cohort study where the investigator selects study subjects, allocates study subjects to receive intervention or comparison intervention, and measures outcomes. The strongest trials use *random allocation* of study subjects to interventions and *blinding* of study subjects and study investigators to intervention. Randomization reduces the influence of confounding by known and unknown factors. Blinding of study subjects, study investigators, and study staff reduces bias in study measurements and confounding in implementation and analysis of study data.

One of the most common types of randomized blinded trials is sponsored by the pharmaceutical industry to evaluate the efficacy and safety of drugs. These randomized blinded clinical trials (RBTs) often compare a drug to an inactive agent, a placebo, or to other currently approved drugs. These designs typically blind study subjects and investigators to the intervention and are described as double-blinded RBTs.

There are two broad categories of randomized blinded trials. In a *between-group design,* outcomes are compared between two or more groups of subjects that are randomly allocated to receive different interventions concurrently. In a *within-group (or crossover) design*, outcomes are compared within a single group of study subjects where individuals receive both (or all interventions) sequentially, but the order of the interventions is randomly allocated. These study designs are examples of *crossover* designs.

Between-Group Design (see Figure 3): Study subjects are randomly allocated to receive intervention or a comparison. Outcomes during the intervention are compared between the two groups of study subjects.

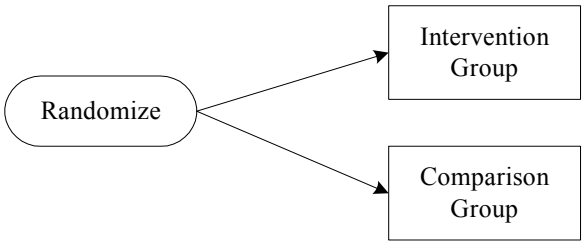

Figure 3. Between-Group Design

Within-Group Design (see Figure 4): Study subjects are randomly allocated to receive either the intervention first followed by a comparison intervention or the comparison intervention followed by the intervention of interest. Outcomes during each intervention period are compared within the entire group of study subjects.

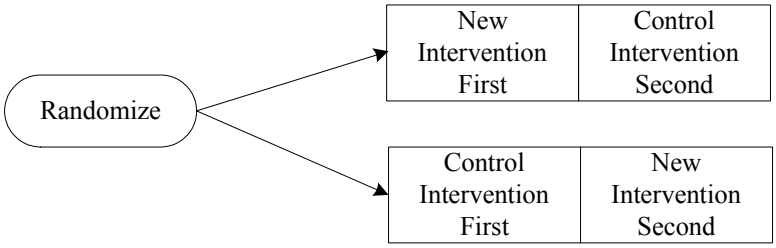

Figure 4. Within-Group Design

There are a variety of ingenious variations in the design and implementation of randomized blinded trials for special circumstances. These include circumstances where there are two or more interventions of interest (factorial designs); there are limitations in blinding study subjects and their providers to the intervention (blinded measurements and blinded analysis); there are special risks or benefits to study subjects from participation (interim analyses of adverse events and outcomes and early stopping rules); or the number of eligible study subjects is small, or recruitment or retention of study subjects poses special difficulties in implementation of the study (unequal allocation of study subjects to intervention groups). The design of randomized blinded trials can be modified to improve the efficiency of randomized blinded trials and reduce error from chance, bias, and confounding. Investigators are encouraged to consult with an epidemiologist or statistician in selecting a study design and in planning a randomized blinded trial.

6.3.2 Nonrandomized Trials

Nonrandomized interventional trials are prospective trials where the allocation of research subjects to interventions is not randomized. In the nonrandomized trial, the intervention or factors of interest may not be directly under the control of the investigator, but the relationship of the intervention to the outcomes is of sufficient interest and importance to be the focus of the study. This may occur in studies of national or state policies, community or organizational programs, natural disasters, or other events. Nonrandomized trials may be used in circumstances where it may not be feasible or ethically permissible to directly allocate individual subjects to interventions, such as an individual's choice of a health insurance plan or high-risk behavior.

In other circumstances, a change in existing technology, drug, device, or program may have occurred. The interventions of interest and the comparison intervention are not both available for concurrent study but are of sufficient interest and importance to study their effects on health outcomes. In these circumstances, it may be possible to compare outcomes after the intervention with outcomes before the intervention in a "before-after" design. These nonrandomized designs have been called "quasiexperimental" designs. Nonrandomized studies with nonconcurrent controls are also subject to confounding due to other conditions or factors that may have occurred between the two time periods. Nonrandomized designs usually do not permit blinding of study subjects or study investigators to the intervention, and hence are subject to bias in data reported by study subjects. Bias can be reduced in the analysis of nonrandomized trials by ensuring whenever possible that the research personnel who collect and analyze data are not aware of the specific intervention the subjects received (blinded analysis).

There are two broad categories of nonrandomized trials, similar to the categories of randomized blinded trials described above. In a *between-group design*, outcomes are compared between two or more groups of subjects that receive different interventions. The different interventions may occur concurrently or sequentially. In concurrent studies, the interventions occur at the same time. This design could be used to study the outcomes of patients who receive care in different health plans in a region, or the outcomes of

patients who reside in different states with different Medicaid programs. Alternatively, the interventions may occur at different times, and the outcomes in groups who receive different interventions are studied. This design could be used to study the outcomes in patients referred for home care after a change in eligibility or payment policies, or the outcomes in patients with acute myocardial infarction admitted to the hospital during a time with shortage in nurse staff or the impact of natural disaster or social or political event such as a terrorist attack on city inhabitants.

In a *within-group design*, outcomes are compared within a single group of study subjects where individuals receive both (or all) interventions. In this circumstance, the individual patients can serve as their own controls. This design could be used to look at patterns of prescription drug use in patients with hypertension after a change from brand name drugs to generic drugs, or a change in payment policies for prescriptions. The nonrandomized *between-group design* is essentially equivalent to a double cohort study, where each group has a different exposure to independent factors analogous to individual study subject risk factors.

Any mechanism of allocation of study subjects to interventions that is not truly random, is a nonrandomized trial and is subject to the same potential problems of bias and confounding that occur in observational study designs. The allocation of study subjects to interventions based on alternate days or times of presentation for care, alternate patients, even or odd patient identifiers, etc., may be consciously or unconsciously manipulated by study subjects, investigators, or others. Such methods have been called "pseudorandomization," but these methods are subject to bias and confounding and are not random methods. Such studies are *not* randomized trials.

Table 5. Interventional Study Designs in Outcomes Research: Randomized and Nonrandomized Trials

Design	Strengths	Limitations
Randomized Trials	• Investigator controls eligibility, exclusion, intervention, and measurements	• May be expensive • Some exposures of interest may not be appropriate, because it is not feasible or ethical to subject persons to the intervention
Nonrandomized Trials	• May be used when a concurrent control is not available	• Patients after the intervention may differ from patients before the intervention in ways that are not known to the investigator and not due to the intervention. • Assumes that except for the intervention, patients before the intervention are similar to patients after the intervention. • Subject to bias due to unknown co-interventions

6.4 The Role of Other Study Designs in Outcomes Research: Integrative Study Designs

Integrative studies (systematic review and meta-analyses, decision analysis, cost-effectiveness analysis, and modeling) complement primary research studies. Systematic overviews and meta-analyses can assist in the planning of the study and preparation of study plan by summarizing current knowledge and identifying gaps in knowledge. Decision analyses can assist in translating the results of studies in practices and policies and applying research findings from one setting to another setting that differs from the original setting and for a different target population.

Outcomes research also includes secondary research designs that complement primary research designs. *Systematic overviews* and *meta-analyses* are methods of selecting, analyzing, and summarizing published research studies to answer research questions and can be used to answer questions about outcomes. Systematic overviews and meta-analyses are especially helpful to investigators in planning the study by summarizing the current knowledge and identifying gaps in knowledge. *Decision analyses, cost-effectiveness analyses,* and *other modeling techniques* are methods for combining, summarizing, and analyzing data from published and unpublished studies, epidemiological and clinical data, and expert opinion, as well as beliefs and values of study subjects, patients, or persons in the population to address clinical, practice, and policy questions that may affect patient outcomes. Decision analyses and related studies are especially helpful to providers, healthcare managers, and policy makers, in translating the findings from outcomes research into practice. Decision analyses and cost-effectiveness analyses can help in implementing programs and policies to improve the structure and processes of care and thereby improve outcomes. The strengths and limitations of integrative study designs are summarized in Table 6.

Table 6. Integrative Study Designs in Patient Outcomes Research

Design	Strengths	Limitations
Meta-analysis Systematic overview	• Use published studies • Explicit search criteria • Uniform data extraction • Wide universe of studies • Assess quality of study • Assess heterogeneity • Combine estimates	• Studies may be heterogeneous • Unpublished studies are generally not included • Primary data may not be available
Decision analysis Cost-effectiveness analysis Simulation study	• Use existing data or expert opinion • Explicit description of outcomes • Distinguish probabilities of outcomes and utilities of outcomes • Powerful methods for identifying important factors • Powerful methods for including costs and outcomes	• Many assumptions in structuring the analysis • Data may not be available • Complexity of model may not reflect actual practice • Difficulty in understanding and disseminating results

6.5 Selection of the Study Design

6.5.1 Common Study Questions and Study Designs

The selection of a study design is based on the type of research question, the resources and time available to conduct the research, and the anticipated use of the answers to the research question. The major factor in the selection of the study design is the type of research question.

One approach is to classify the study question into one of four common types of study questions and consider using the study design that has been most frequently and successfully used for each type of question: (1) *diagnosis* and other descriptive studies of processes and outcomes; (2) studies of *etiology* (causation); (3) studies of *prognosis*; and (4) studies of *therapy* (see Table 7).

Studies of *diagnosis* address important processes of care and affect patient outcomes. Diagnostic test evaluation studies describe the diagnostic accuracy (diagnostic sensitivity, diagnostic specificity, positive predictive value, negative predictive value), safety, and cost of tests. These studies describe the

relationship of the test result to the presence of disease at the time the patient test is performed or at the time a biologic specimen is obtained. Many studies of diagnostic tests are therefore a type of a cross-sectional study design. These studies may include information on the use of other health services and information on patients' outcomes. Observational studies such as cohort studies and interventional studies such as randomized blinded trials may also be used to study the relationship between a diagnostic test and patient outcomes.

The second type of study question focuses on the identification of factors associated with the occurrence of disease (risk factors). Factors associated with the cause of the disease are often described as etiologic factors and are described as studies of *etiology* or studies of the cause of disease. Case-control studies and cohort study designs are generally selected for studies of etiology. A cohort study has advantages when a small number of factors are of interest, the interval between exposure to the factor and the outcome is short, and the outcomes are relatively frequent. Case-control study design has advantages when there are many factors of interest, the outcomes are rare, and the interval between the exposure to the factors of interest and the outcomes are longer.

A third type of study question addresses factors associated with the outcomes of disease (prognostic factors). These studies investigate the clinical course of a disease or condition (the *prognosis* of a disease). Traditionally, the outcomes are due to the nature of the disease. The outcomes of a disease will depend on the patient characteristics, the disease or condition, and the treatments and health services received. The health outcomes of study subjects with one or more characteristics, conditions, or who have received specific medications, specific laboratory or other tests, or who have received other specific health services in the usual clinical or community setting are best evaluated in a cohort study. Cohort studies are especially useful when there are many outcomes of interest and can be used to assess clinical outcomes, health-related quality of life, patient preferences for health outcomes, and resource use. The focus of these studies is on the relationship of the characteristics of the patient and the disease to the outcomes, not on the efficacy of the treatment in changing outcomes. A follow-up study of patients who have received a treatment is a study of prognosis. A comparison of the outcomes of a cohort of patients who have received a treatment with the outcomes of a cohort of patients who have not received a treatment is a nonrandomized double cohort study, and should be thought of as a study of treatment. This study design is more subject to confounding than a randomized blinded trial. Cohort study designs are generally selected for studies of prognosis, and can also be used to study treatment.

The fourth type of study question focuses on *therapy*. This study question includes the effectiveness of drugs, devices, and other procedures in treating disease, as well as the effectiveness of drugs, devices, and other procedures in preventing disease. The effectiveness of a therapeutic intervention is best evaluated in a randomized blinded trial. Concurrent study of two or more groups (a between-group design) is preferred when an adequate number of study subjects are available and can be allocated to each intervention group. In within-group designs, two or more interventions are allocated to each study subject in random order. Within-group study designs are useful when study subjects are difficult to recruit and enroll, and the study subjects return to the baseline preintervention state after each intervention. Nonrandomized trials are possible when it is not feasible or ethically permissible to allocate study subjects to interventions, and are especially useful when studying natural disasters, programs, or policy interventions. For studies of the efficacy or effectiveness of preventive and therapeutic interventions, a randomized blinded trial design is generally selected.

Table 7. Type of Research Questions and Suggested Study Designs

Type of Study	Suggested Design	Alternative Study Designs
Diagnosis	Cross-sectional study	Case-control study
Causation	Cohort study	Case-control study Nonrandomized trial
Prognosis	Cohort study or nonrandomized trial	Randomized blinded trial
Therapy	Randomized blinded trial	Nonrandomized trial Cohort study

6.5.2 An Algorithm for Selecting a Study Design

An alternate approach in the selection of the study design is to consider the answers to three questions: (1) does the investigator plan to intervene to alter the current processes of care? (2) Does the study question require the observation of events over time? (3) Can the study question be answered by analyzing currently available information on current and past characteristics of study subjects, or will the investigator be required to follow study subjects prospectively to study events that have not yet occurred? An experimental study, either a randomized blinded trial (RBT) or a nonrandomized trial will be required if the study question requires the investigator to alter the current processes of care. If the study question does not require the investigator to alter the processes of care, an observational study design may be considered. If the study question does not require the observation of events over time to make causal inferences about the sequence of events, then a survey or cross-sectional study design may be selected. If the study question requires an examination of the sequence of events over time, then either a case-control or cohort study design may be selected. If information of acceptable quality is available on the current and past characteristics of study subjects and one or more health outcomes, then a retrospective cohort study or case control study design may be selected; otherwise, a prospective cohort study will be selected (see Figure 5).

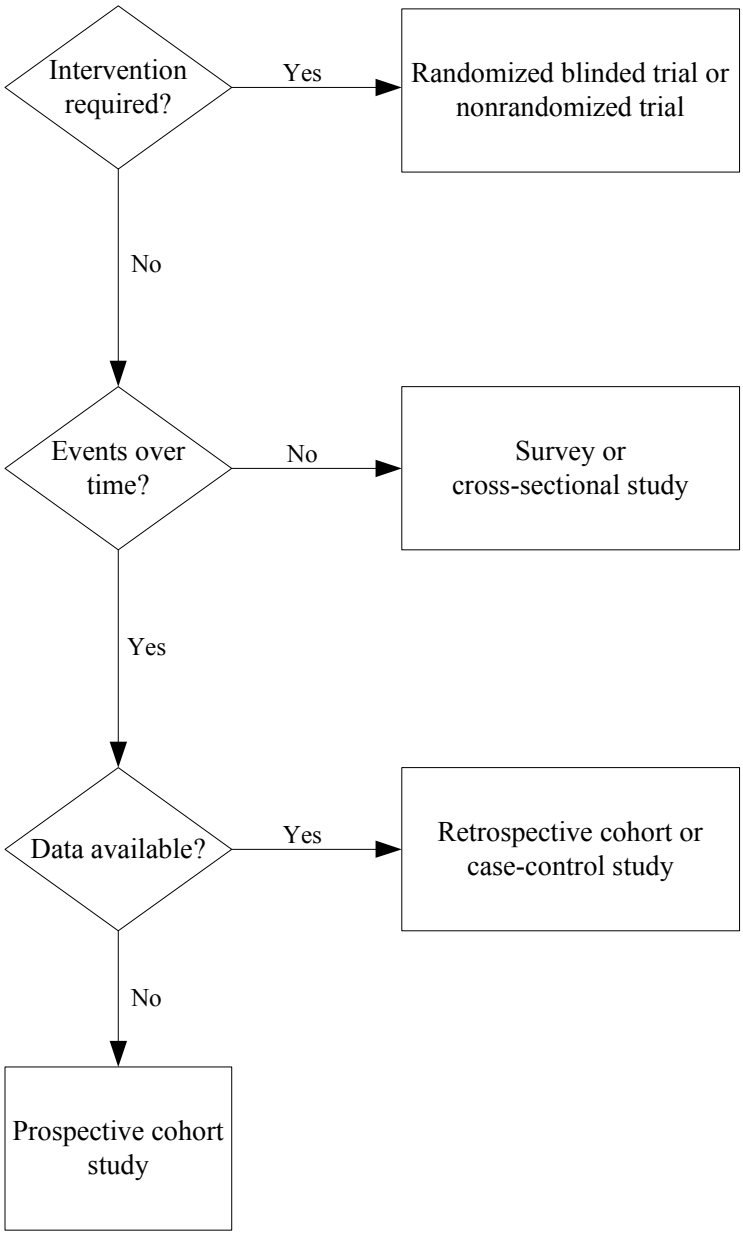

Figure 5. Simple Algorithm for Selecting Study Design Based on Three Questions

The observational and experimental study designs available to answer research questions about patient outcomes differ in the resources required, the time to complete the study, and susceptibility to bias and confounding. Increasing the sample size can reduce chance as a source of error in patient outcomes research. This, however, will generally increase the cost and often the time required to complete a study. The magnitude of increased cost and time will vary by study design and other factors. As a result, investigators must consider the anticipated use of the answers to the research question and inferences based on the findings of the research study in the selection of the study design.

Descriptive studies and studies to explore potential risk factors for the occurrence of disease or prognostic factors for outcomes may be used to plan additional research studies, manage the processes of care, develop guidelines for clinical practice, or develop programs and healthcare policy. In circumstances

where resources are limited; results are needed sooner; the risks are small in relation to the benefits of implementing changes in practice based on the study findings; and the costs of implementing changes are small or there are savings in cost of services; small studies, observational study designs, case control studies, or retrospective cohort studies may have advantages. In circumstances where the information is required to provide definitive understanding of the mechanisms of disease; the efficacy of preventive and therapeutic interventions; or the safety and effectiveness of drugs and devices prior to regulatory approval for sale and marketing; or the costs of implementing the study findings are high; larger studies, randomized blinded trials, or prospective cohort studies may be required.

Prospective investigators should understand that often, the selection of study design is a pragmatic decision made to maximize the internal and external validity of inferences based on the study that can be completed within the available time using the available resources. In any research program, one or more study designs may be used to address a series of interrelated research questions.

6.6 Study Subjects and Study Setting

The study subject and study setting issues that are important in outcomes research are the definitions of the target population, eligible population, and enrolled population; the characteristics of study setting and study subjects that affect their eligibility and participation in outcomes research; the number of study subjects; and potential sources of error and methods to minimize error.

6.6.1 Target Population, Eligible Study Subjects, and Enrolled Study Subjects

The goal of patient outcomes research is to produce valid, generalizable knowledge of the factors associated with patient outcomes. In this regard, patient outcomes research is similar to clinical research and all scientific research aspiring to identify knowledge and principles that are valid and useful, not only for the actual subjects enrolled in a specific study, but also in the care of future patients at the same site in which the study was conducted and, most importantly, in other sites as well.

Target Population: The target population is the group of persons about which inferences will be made about the validity of study findings. The population may be persons with specific characteristics or who may receive specific services and experience specific outcomes. For example, based on a published study, it may be concluded that elderly patients do not require medical testing prior to elective cataract surgery to reduce serious complications of surgery.

Eligible Population: The eligible population is the subset of study subjects with characteristics relevant to the study question who are likely to receive the healthcare service or process of care of interest and are at risk of experiencing the outcomes of interest. The eligible population will usually be a subset of all persons in the reference or target population selected, based on scientific issues related to the study questions, intervention, measurements, and outcomes, as well as practical issues related to the feasibility of the study and efficiency of conducting the study.

Enrolled Population: The enrolled population is the group of study subjects from the target population who are screened for eligibility, meet the eligibility and exclusion criteria, and are selected for inclusion in the study. In prospective studies, these enrolled study subjects will usually have given informed consent to participate in the study. Ideally, all study subjects who are enrolled in a study will complete the study protocol and all follow-up study measurements. Study subjects who withdraw from a study (dropouts) or who are not available or refuse to participate in follow-up measurements of study outcomes (loss to follow-up) are included in the enrolled population. Findings from these study subjects should be analyzed to the extent possible and included in all reports from the study.

Investigators therefore should explicitly identify the *target* population about which inferences will be made concerning the relationship of the factors studied to the patient outcomes. Investigators must

explicitly identify the characteristics of the study subjects—patients—who are eligible to be included in the study. Scientific criteria, practical constraints, and ethical principles may require that subjects with certain characteristics be excluded from the study. These should be explicitly stated in the study protocol. The eligible population will be a subset of the target population. The eligibility and exclusion criteria are established by the investigator, based on the appropriateness of study for addressing the study aims, safety (risks of intervention in relation to benefits), and efficiency of study (responsiveness to intervention, minimizing confounding factors). The enrolled study subjects are those persons in the target population who are eligible for the study, are contacted and invited to participate, give informed consent, and actually participate in the study.

The internal validity of the study will depend on the findings in those who are eligible and enrolled into the study. The external validity (generalizability) will depend on the extent to which those enrolled reflect the target population. Systematic differences between the reference population, the eligible population, and enrolled subjects (selection bias) may contribute to erroneous inferences about whether the study findings in the enrolled subjects may be generalized to the target population.

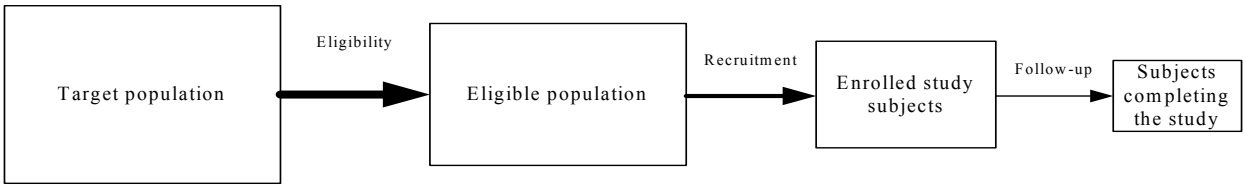

Figure 6. Target Population, Eligible Population, and Study Population

6.6.2 Eligibility and Exclusion Criteria

A key issue for prospective investigators is to identify both the characteristics of the target population for whom inferences will be made, as well as the *eligibility* and *exclusion criteria* used to select the actual patients enrolled in the study. Investigators should make the eligibility criteria as broad as possible and the exclusion criteria as limited as possible.

In clinical research, the goal is often to make generalizable insights about the *efficacy* of the specific device or drug to achieve a specific change in a clinical or physiologic measurement. In this context, issues related to the efficiency of the study design will motivate investigators to choose selected populations, so the efficacy of the device or drug or intervention can be studied with the most efficient use of investigator resources and minimum number of study subjects. In contrast, studies of patient outcomes are often designed to make generalizable insights about the *effectiveness* of specific devices, drugs, or practice policies in the context of the usual setting in which patients live, work, and receive care. Therefore, in patient outcomes studies, investigators should have as large a target population as possible and as inclusive eligibility criteria as possible, and exclude as few subjects as possible; ideally, no study subjects would be excluded.

6.6.3 Characteristics of Study Setting and Study Subjects

To assist in the assessment of the validity of outcomes research, the study should report the following information about potential sources of bias and confounding factors: (1) demographic characteristics; (2) socioeconomic status; (3) social factors; (4) health-related behaviors; (5) community setting; (6) clinical characteristics; (7) comorbid conditions; and (8) health system characteristics where the study was conducted.

A broad array of factors beyond those usually considered in clinical research may potentially be important in the selection of study subjects: the study subjects' baseline characteristics; the study subjects' ability to comply with the study protocol; the efficacy of the intervention; retention of study subjects in the study; and the measurements of outcomes. These factors may contribute to bias and confounding. Investigators should consider these factors in the design and implementation of the study to reduce bias and assess their potential role as confounding factors. Investigators should consider the study subjects and the study setting characteristics listed in Table 8.

Table 8. Potential Sources of Bias and Confounding in Information About Study Subjects and Study Setting

Category	Examples
Demographic	• Age, sex, race, ethnicity
Socioeconomic status	• Education, income, occupation • Occupation and job title • Currently working, unemployed seeking work, homemaker, retired • Gender differences in working for wages or working at home • Racial/ethnic differences in education
Social factors	• Marital status • Family size and structure • Social support • Living at home
Health-related behaviors	• Diet, alcohol, and other drugs • Preventive services and screening • Exercise and sedentary behavior • Seatbelts, bicycle helmets, storage of handguns
Community setting	• Urban, suburban, rural community • Access to public transportation • Distance to providers and healthcare facilities • Air and water quality • Environmental factors
Clinical characteristics	• Diagnoses and conditions for eligibility and outcomes • Severity of illness (e.g., cancer stage, grade, histology or hypertension with end organ damage involving kidneys, eyes, blood vessels) • Other medical conditions
Comorbid conditions	• Charleson comorbidity index for hospital patients • APACHE (Acute Physiology and Chronic Health Evaluation) score for ICU patients
Healthcare system	• Providers (physicians, primary care and specialists, nonphysician providers) • Facilities (ambulatory, acute-care hospital, long-term care) • Organization • Managed care organization • Healthcare financing

6.6.4 Estimating the Number of Study Subjects Needed

Outcomes research requires time, money, resources, and may expose study subjects to risks. Outcomes research should therefore study only as many subjects as needed to answer the study questions, and duration should be as short as possible. This will ensure that the resources will be used efficiently to minimize risk and maximize benefits to the subjects enrolled in the study. This will also ensure that future persons will benefit from the study findings; avoid inappropriate, unnecessary, or harmful services; and receive necessary, beneficial services that may improve outcomes.

The subjects enrolled in the study can be considered a sample of eligible subjects. The number of subjects needed to demonstrate differences in outcomes (or no difference) can be described as the *sample size*. All outcomes research should be planned with estimates of sample size. Sample size estimates are best made

in consultation with an epidemiologist or statistician. The sample size will depend upon the study goals and study question, study design, types of measurements, anticipated value and variation in outcomes, and the investigators' judgment about the magnitude of differences in outcomes or risk factors that are anticipated to occur or important to detect. The estimates of the magnitude of differences between groups that would be important in hypothesis testing, as well as the acceptable magnitude of errors in making inferences about differences between groups are judgments made by investigators, clinicians, sponsors of the research, and policy makers based on the state of scientific research, clinical practice, health services, health policy, and other issues. These decisions are complex and balance concerns about ethical issues related to research subjects, resources and time to complete a study, and the intended use of study findings.

Baseline values for sample size estimates may be obtained from expert opinion, published literature, other experienced investigators, or prior research on the same question in the same study setting, or even feasibility studies designed to provide these estimates for a more definitive study. The sample size of a study can be increased by increasing the study duration or by increasing the number of study sites. Allowances should be made for dropouts and losses to follow up.

Sample size estimates and assumptions should be explicitly stated in written protocols and subjected to peer review. Sample size estimates are inherently uncertain, and it is often useful to include a range of estimates for any uncertain baseline estimates and variations in estimates. These may be displayed as tables or graphs of sample size over a range of estimates.

The sample size estimates will be used in planning the number of study subjects to screen for eligibility, the number to be enrolled, the study personnel and other resources, study duration, and study budget. Study protocol budget, resources, and facilities are best planned in consultation with an administrator, or manager familiar with study setting and financial management of research programs.

Table 9. Relevant Factors in Estimating Sample Size

Factor	Example
Study goals	Demonstrate difference or equivalence
Study design	RBT of surgical or medical therapy Case-control study to identify risk factors
Number of eligible study subjects and number of study subjects with outcomes	Prevalence of disease in target population Incidence of outcomes in target population
Anticipated difference and minimal difference to detect	Detect a 4-mm Hg difference in blood pressure or 25% reduction in complications
Baseline measurements	Untreated systolic BP: mean 145; standard deviation 5 Complications in 1 per 1000 persons
Number of independent variables	Five risk factors (age, sex, hypertension, cholesterol, family history)
Number and type of outcomes	Death, nonfatal myocardial infarction, angina, hospital admission, survival time, hospital charges
Types of variables	Blood pressure or number of persons with elevated blood pressure
Acceptable magnitude of errors in inferences	5% Type I error 80% power (20% Type II error)

6.7 Measurements

Investigators should understand the types of variables (continuous, categorical ordinal, or categorical cardinal) and the types of outcomes (counts, measurements rates, and time to events), as these will impact summary statistics, types of statistical tests, sample size, study duration, and cost.

Patient outcomes research focuses on the identification of factors associated with patient outcomes and the development, testing, and dissemination of effective methods of health care to improve patient outcomes. The assessment of the factors related to the outcomes and the assessment of the outcomes is therefore a central issue in outcomes studies. The information on patients, their health, and the health services and their outcomes may be different for individual study subjects, may change over time, and are described as study variables. The variables that describe the patient characteristics, disease characteristics, health-system characteristics, and health services can be collectively termed "independent variables" and the variables that describe the outcomes can be collectively described as the "dependent variables."

6.7.1 Types of Data

Variables may be *continuous* (measurements) or *categorical* (counts). The categorical variables may be dichotomous (two categories) or have more than two categories. Categorical variables may be cardinal with no specific order (e.g., ABO blood groups) or ordinal in which there is specific order in the categories based on some characteristic or criterion (e.g., excellent, very good, good, fair, or poor self-reported health status). For example, in clinical chemistry, a blood glucose concentration is a quantitative measurement; urine dipstick for glucose, measured as 1+, 2+, etc., is a semiquantitative measurement that would be described by statisticians as an ordinal categorical variable; a urine pregnancy test would be considered a qualitative measurement that would be described by a statistician as a dichotomous categorical variable.

The type of variable, continuous or categorical, and the type of categorical variable (cardinal or ordinal) will affect the type of measurements, precision in assessments of baseline differences and outcomes, description and summary of study findings, statistical tests to be used in analysis, and sample size needed to test hypotheses and estimate precision of results. These will also affect the resources, costs, and time needed to complete the study and answer the study questions. Therefore, investigators will need to understand the nature of study variables in design of an outcomes study.

6.7.2 Formats for Describing Outcomes

There are four formats for describing outcomes that are used in outcomes studies: *counts*, *measurements*, *rates*, and *time to the occurrence of an outcome* (a "failure time" analysis). Counts are categorical variables; measurements, rates, and time to an outcome are continuous variables.

Table 10. Types of Variables and Associated Analyses

Outcomes Format	Definition	Descriptive Statistics	Statistical Tests	Multivariable Methods
Counts	Number of study subjects with a characteristic or an outcome	• Count and proportion • Prevalence	• Chi-square	• Logistic regression
Measurement	Amount or quantity	• Mean, SD, range • Median, quartiles, inter-quartile range, range	• T-test • Non-parametric tests	• Linear regression • Non-linear regression
Rates	Counts of study subjects or persons with an event or outcome per amount of time	• Incidence rates	• Incidence rate ratios	• Mantel-Haenszel stratified analysis • Logistic regression
Failure Time	Time to an event or outcome	• Survival time • Hazard rates • Life table • Survival (%) at specific time	• Kaplan-Meier survival curve • Logrank test	• Cox proportional hazards regression

6.7.3 Outcome Domains

Investigators should study a wide range of relevant clinical outcomes in patient outcomes research. Investigators are strongly encouraged to include health-related quality of life, preferences and costs in patient outcomes research.

In general, each of the four types of outcomes variables could be used to describe any health outcome. Health outcomes encompass a broad range of outcomes that can be classified into four groups: (1) clinical and functional outcomes; (2) health-related quality of life; (3) preferences for health; and (4) resource use and costs. A distinguishing feature of outcomes research is the inclusion of several outcomes from one or more of these domains in a single study.

Clinical outcomes and functional outcomes should include activities of daily living, instrumental activities of daily living, and other relevant condition-specific or disease-specific and generic measures of activities, in addition to the clinical measurement usually used in clinical practice.

Health-related quality of life should be assessed whenever possible, using questionnaires that have previously been shown to be reliable, valid, and responsive to clinical and other interventions. Generic measures such as one of the Medical Outcomes Study short form (SF-36) measures,[19] the Quality of Well-Being Scale,[20] the EuroQOL,[21] or similar measure, and any relevant disease- or condition-specific measures are suggested. The SF-36, for example, assesses eight health concepts: limitations in physical activities, social activities, and role activities because of health problems, pain, general mental health, vitality, and general health perceptions.[19] Investigators are encouraged to review the literature on these outcomes research measurements to assess their strengths and limitations in light of the types of measurements needed and the types of outcomes of interest.

Preference-based measures of health are suggested, as appropriate, for outcomes studies. These preferences can be obtained in patient interviews by trained research staff.

Measures of resource use and costs should be included whenever possible. The study should indicate perspective of analysis, and whenever possible, recorded healthcare costs from a societal perspective. Cost and resource use should include, at a minimum, direct medical costs for healthcare services. In addition, direct nonmedical costs such as payment for babysitting, transportation, parking, or lost wages, as well as intangible costs, may be included in estimates of the costs in outcomes studies.

Table 11. Outcomes Domains and Measures

Domain	Measures	Examples
Clinical and Functional Outcomes	Vitals signs	Pulse, blood pressure, respiratory rate, temperature
	Physical examination	Muscle strength
	Imaging tests	Tumor size on computed tomogram
	Laboratory tests	Cholesterol
	Organ physiology	Ejection fraction by echocardiogram
	Activities of daily living	Eating, toileting, dressing, bathing, transferring from bed to chair, and walking
Health-Related Quality of Life	Generic measures	Short form-36 (SF-36)
	Disease-specific measure	N.Y. Heart Association classification for heart failure
Preferences or Utilities	Utility or preference for current health	Standard gamble assessment of health as percentage of perfect health
Resource Use or Cost	Costs	Hospital charges, out-of-pocket payments, lost wages

6.8 Interventions and Follow-Up

Investigators should study the effect of clinical interventions and practice policy interventions on patient outcomes.

Clinical Interventions: Two broad classes of interventions may improve patient outcomes and may be the focus of patient outcomes research studies. The first class of interventions consists of clinical interventions that are the central focus of most clinical research and include new laboratory or imaging tests or other diagnostic tests, new devices used in clinical care, new pharmaceutical agents for prevention and treatment, and new procedures such as surgery, physical therapy, chiropractic manipulation, acupuncture, and other procedures for treatment of specific conditions.

Program or Policy Interventions: The second class of interventions consists of program and policy interventions. This broad class of interventions may include newly available drugs, devices, or procedures in the usual practice setting, but also new, improved, or more efficient policies for using existing drugs, devices, and procedures. These practice-based interventions and practice policies may consist of new algorithms for the diagnostic evaluation of patients with suspected disease, new screening programs, alternative patterns of follow-up, selected referral of patients, or the implementation of practice guidelines and clinical pathways.

Unit of Intervention: A particular theme that is important in the design, conduct, and interpretation of patient outcomes research is the unit of intervention. In most clinical research, a specific device, drug, or

procedure is tested to determine whether its application improves clinical and functional outcomes in individual patients. In the strongest research designs, individual patients are randomly allocated to receive the new drug, device, or procedure being studied or a comparison (usual care, current device, or placebo) intervention. Ideally, the care of patients who do not receive the innovative intervention will be identical to the care of patients who receive the comparison intervention. In practice, however, many interventions are complex and when used in clinical settings, patients and clinicians may be aware of the intervention. This in turn, may influence the care of patients who do not receive the intervention or may influence the measurement of the outcomes. The latter problem can be avoided by having blinded outcomes assessment by an investigator or member of the research team who is not aware of the study hypothesis or the interventions received by the patients. It may be necessary to intervene in all of the patients cared for by a specific provider, or for all of the providers in a clinic or hospital. Thus, even in studies of clinical interventions, the individual patient may not be the most effective unit of intervention for patient outcomes research. In studies of practice policies, it is customary for policy to be implemented in a setting where multiple patients receive care from individual providers, or several providers care for many patients in the same setting. Patients of the providers in the setting in which the practice policies are implemented are more likely to receive the specific intervention or have different care compared to the care of the patients of physicians working in settings where practice policies are not being implemented. The usual design for the study of practice policies will consist of one or more physicians, clinics, hospitals, or centers allocated to receive an innovative intervention and one or more physicians, clinics, hospitals, or centers to receive a comparison intervention. Thus, in some clinical research and in most studies of practice policies, the unit of intervention may not be the individual patient but rather groups of patients grouped by physician, clinic, hospital, or other setting. In such studies, other patients grouped by physician, clinic, and hospital may serve as a comparison or "control" group. In this case, the design, implementation, and analysis of the patient outcomes research must account for the unit of intervention and the effect of the grouping of patients by physician, clinic, and hospital.

The unit of intervention may be an individual person or a patient, or physician, clinic, hospital, or other group. A physician, clinic, hospital, or other group may have multiple patients who are enrolled in the study. The design and analysis should account for the grouping of patients by provider, clinic, or hospital. The unit of intervention and grouping should be described and plans made to account for this grouping in the analysis.

6.8.1 Sources of Error and Strategies to Reduce Error

The outcomes study design should include measures to ensure high rates of adherence to study intervention, especially if the intervention takes place over time. The study should report adherence to the study intervention, dropouts, crossovers, and losses to follow-up.

In randomized controlled clinical trials and other outcomes studies where the intervention is directly allocated by the investigator to study subjects, the essential issues are adherence to the study intervention in the group allocated to the intervention and assessing whether the comparison or control group has not received the study intervention. Adherence to the study intervention is especially important when the intervention takes place on more than one occasion or over a long period of time. In randomized clinical trials of drugs, for example, a key issue is assessing study subject (patient) compliance with medication regimen over time. There are several methods that can be used to ensure a high level of study subject adherence to study intervention. Some are adapted from clinical practice (such as simplifying the regimen, reminders); others (such as nonmonetary incentives) are not used in clinical practice.

Investigators should ensure that the comparison or control group has not received the intervention. This is sometimes referred to as "contamination" of the control group. For example, in a randomized controlled trial of preoperative screening, the control group should not receive the screening tests that are being studied. If anyone in the control group receives the intervention, the power of the study to detect differences in outcomes is reduced.

Investigators should include procedures to minimize the likelihood that the study subjects will not complete the study. Dropouts and losses to follow-up may occur for many reasons. They may result in bias if they occur more frequently in study subjects who receive specific interventions or with specific characteristics. This may occur, for example, when subjects drop out of a study due to adverse effects of an intervention.

Even if dropout or loss to follow-up is not different between study groups, a study can be compromised because of the reduced sample size and power to detect differences between study groups. Dropouts and losses to follow-up can increase the chances of a Type II error when interpreting the results of the study.

6.9 Analysis

6.9.1 General Principles

The analysis of an outcomes study should be conducted by a statistician in consultation with the principal investigator and co-investigators. Investigators should consult with epidemiologists and statisticians during the design of the study and prior to the analysis. The references contain a list of textbooks, software, and information that may be useful in analyses of outcomes research.

While there is no standard format for presentation of the study analysis in general, a description of the analysis of findings of the research studies is included here with the expectation that investigators would appropriately modify the analysis for each of the individual patient outcomes research studies.

- The analysis of findings from patient outcomes research studies must be appropriate for the study aims, type of study design, study measurements, and interventions. The analyses may include both qualitative description of the study implementation and findings as well as quantitative analysis of study findings.

- Investigators should be aware of the nature of measurements (continuous or categorical measurements, etc.) and summarize the variables by including information on central location, dispersion, and range. Investigators should use measures appropriate for normally distributed and skewed variables, including means and standard deviations for variables that are approximately normally distributed, and consider medians, interquartile range, and quartiles for skewed variables.

- Investigators should report and analyze all available data. Any missing data should be explained, and exploratory analyses should be performed to ascertain if the pattern of missing data may result in bias.

- The analyses should be appropriate for the types of variables in the study and the format for the outcomes. For example, Chi-square test and logistic regression may be used for categorical variables. T-tests and linear regression are appropriate for continuous variables, and Kaplan-Meier survival methods and the Cox proportional hazards model are appropriate for time-to-event variables (see Table 10). Appropriate univariate statistical tests for the differences between groups should be conducted. In general, parametric methods should be used for normally distributed variables, and the underlying assumptions for parametric testing should be examined. Nonparametric tests should be used for variables that are not normally distributed. In consultation with a statistician, investigators may choose to use normalizing transformations for skewed variables, so the methods of analysis can meet the underlying assumptions to ensure valid application of statistical tests using parametric methods.

- Assembly of the study population should be reported, including the number and characteristics of persons screened and enrolled and the number of persons excluded and reasons for exclusion. Any information about characteristics of persons excluded should be reported when available and ethically permissible. The baseline characteristics of study subjects should be described.

- The study analysis should include descriptive statistics and summary data of the characteristics of the patient populations enrolled in the study. These data are typically presented in an initial table. A common format would describe characteristics of the patients in the study groups and the essential subgroups in one or more columns, and the relevant initial or baseline demographic, clinical characteristics, comorbid conditions, and other factors in each row. In a case control study, the table may include characteristics of the cases and the controls while in a cohort study, and may include the characteristics of the exposed and nonexposed members of the cohort for the most important categories of exposure. For a randomized, controlled trial, the table may include the characteristics of the groups to which the study subjects are allocated, such as the "intervention" group and the "comparison" group.

- Study implementation, intervention, and follow-up should be analyzed and reported. Outcomes research analysis should use the "intention to treat" principle for studies of interventions. Adherence to study protocol, withdrawals from study, dropouts, and loss to follow-up should be reported.

- The analysis should be appropriate for the unit of intervention.

- The intention to treat analysis should be used in studies of interventions. The patient outcomes will be measured for all subjects or patients who are allocated to the group intended to receive the intervention, and for all subjects or patients who are allocated to the group intended to receive a comparison intervention.

- Outcomes for all relevant study groups should be reported. Patient outcomes should be described, including absolute and relative outcomes. Measurement of individual outcomes in each domain should be described. Summary measurements constructed for statistical tests and the type of test should be described. Investigators should describe the major outcomes measurements (clinical outcomes, health-related quality of life, utilities, and costs) for each of the major patient groups. For example, in an RBT report, outcomes in each group (number, number who experience an endpoint, time to endpoint, or an endpoint measurement) as well as summary measures used in analysis (risk ratio, risk differences, relative rate reduction, hazard ratios, etc.) would be reported.

- Subgroup analysis: Investigators should be cautious in making inferences about findings based on post-hoc analysis of subgroups.[22]

- Multiple comparisons: Investigators should be cautious in accepting the validity of statistical tests of significance when multiple comparisons are performed. Multiple comparisons, and comparisons of subgroups, are more likely to result in statistically significant tests, even when there are no true differences. One approach to minimize the likelihood of Type I errors is to specify all planned analyses (including multiple comparisons) and subgroup analyses in advance, at the time the study is planned. Investigators are encouraged to review these topics[22-40] and to consult with a statistician.

- Exploratory analyses (data mining) may be useful to generate hypotheses for future studies. Investigators should be cautious in making inferences from data mining where large sample sizes inevitably result in statistically significant P-values.

6.9.2 Assessing Chance

The statistical tests used to test hypotheses should be appropriate for the type of variable. The selection of parametric tests or nonparametric tests must be appropriate for the distribution of the variables. To assess the role of chance, hypothesis tests, statistics, and P-values should be reported. Estimates of the magnitude of the effect and confidence intervals should be reported. A multivariate method for analysis should be used to test for differences in groups and adjust outcomes by groups.

6.9.3 Assessing Bias

Information to assess the occurrence of bias should be included whenever possible. There are two major potential types of errors that may occur in the design and analysis of patient outcomes research: bias and confounding. Epidemiologists have specific expertise in addressing potential biases and confounding study design and study analysis. Bias is a type of error that occurs when the study measurements systematically differ from the intended measurements. In patient outcomes research, bias most often occurs when the patients in the target population differ from the patients who are available for study, selected for the study, or enrolled in the study. Thus, the patients and the measurements from these patients may differ systematically from the target population. If the patients in each group studied differ systematically as a result of the methods of selecting patients for study or allocating patients to study groups, then the difference may reflect bias and not true differences. The investigator may not be aware of these differences and the potential for bias at the time patients are selected for the study, enrolled in the study, or at the time when baseline measurements or the outcomes measurements are made. Unless measurements are made from the target population, or from eligible patients not enrolled in the study, the occurrence and magnitude of bias cannot be directly studied. Accordingly, it is important to anticipate bias and control for the occurrence of bias in the design of outcomes research, as it is generally not possible to control for bias in the analysis.

6.9.4 Assessing Confounding

Another type of error that may occur is confounding. Confounding can occur due to factors that are associated with the independent variables or risk factors of interest of the study subjects, and it is also associated with the patient outcomes of interest. The role of potential confounding can be accounted for in the analysis if information about the potential confounding variables is collected as part of the study. The role of potential confounding factors cannot be assessed if information is not collected on potential confounding factors. It may not be possible to collect information about potential confounding factors that are identified by other investigators or peer reviewers of manuscripts after a study is completed. Accordingly, investigators are strongly encouraged to consider a wide range of potential confounders and collect information about them so they will be able to respond to questions from other investigators, colleagues, and reviewers of manuscripts submitted for publication. Methods that can be used in the design and analysis to control for confounding include restriction, matching, stratification, and multivariate analysis.

7 Reporting Outcomes Research

7.1 Overview of Reporting

Ideally, all patient outcomes research should be reported and disseminated so that other patients, providers, and investigators may benefit from the research. Publications must indicate the role or lack of a role of the study's sponsor(s) in (a) study design(s), data acquisition, data analysis (and interpretation), and the preparation of the report and the decision to publish the work. Ordinarily, patient outcomes research will be submitted for review, published in the peer-reviewed professional literature, and disseminated to the health services research community and healthcare providers. However, there are many other potential vehicles to disseminate patient outcomes research findings to ensure that the research actually improves patient outcomes. Other methods of disseminating the findings of patient outcomes research include professional organizations, provider organizations, and the lay press. A variety of media other than print media are available including radio, television, and the Internet.

Unfortunately, not all patient outcomes research studies are successfully implemented and not all studies result in successful interventions or statistically significant differences in the groups studied. Reports of such studies may not be published because of limited resources, unanticipated difficulties in implementing or completing the research, or the rejection of reports based on criticism of studies by peer

reviewers. Publication in the peer-reviewed literature is important in ensuring that the study design, implementation, analysis, and findings receive rigorous review and scrutiny by qualified reviewers. Peer review helps assure readers and users of patient outcomes research that findings are valid and generalizable. If a patient outcomes study is not accepted for publication in the peer-reviewed literature, the investigators should revise the study report and resubmit to the same journal, if invited by the editors to resubmit, or submit the report to another journal that is perhaps more focused on patient outcomes research, the type of intervention, or the patient population studied.

Investigators have an ethical obligation to other investigators and patients to disseminate the results of their studies to the widest population so patients may benefit from the findings. While it is important to report the results of all studies whether positive or negative, it is especially important to report the findings of the studies that do not find statistically significant differences in outcomes. A particular concern is the often cited but rarely documented problem of "publication bias" in which studies which failed to find statistically significant differences are thought to have increased difficulty in being accepted for publication in the peer-reviewed literature, with the consequence that the published studies are a biased sample of all patient outcomes studies.

7.2 Reporting Studies of Diagnostic Accuracy

In general investigators reporting patient outcomes studies should follow the *Uniform Requirements for Manuscripts Submitted to Biomedical Journals* guidelines. Investigators should consult the "Information for Authors" of the journals to which they would like to submit the patient outcomes study for publication for guidance on whether or not the patient outcomes study is appropriate for the journal. Investigators should review the specific information for the preparation of the manuscript as a first step in preparing the manuscript for publication. Editors of peer-reviewed journals have fostered the development of guidelines for investigators to use in reporting studies of the diagnostic accuracy of tests and the results of trials of interventions.

Investigators should follow the recommendations for the Standards for Reporting of Diagnostic Accuracy (the STARD statement; see Table 12 and Figure 7).[41]

Table 12. STARD Checklist of Items to Include in Diagnostic Accuracy Study. (From Bossuyt PM, Reitsma JB, Bruns DE, et al. Towards complete and accurate reporting of studies of diagnostic accuracy: The STARD initiative. Standards for Reporting of Diagnostic Accuracy. *Clin Chem*. 2003;49:1-6. Reprinted with permission from the American Association for Clinical Chemistry.)

Section and Topic	Item #		On page #
TITLE/ABSTRACT/ KEY WORDS	1	Identify the article as a study of diagnostic accuracy (recommend MeSH heading 'sensitivity and specificity').	
INTRODUCTION	2	State the research questions or study aims, such as estimating diagnostic accuracy or comparing accuracy between tests or across participant groups.	
METHODS		Describe	
Participants	3	The study population: The inclusion and exclusion criteria, setting and locations where the data were collected	
	4	Participant recruitment: Was recruitment based on presenting symptoms, results from previous tests, or the fact that the participants had received the index tests or the reference standard?	
	5	Participant sampling: Was the study population a consecutive series of participants defined by the selection criteria in items 3 and 4? If not, specify how participants were further selected.	
	6	Data collection: Was data collection planned before the index test and reference standard were performed (prospective study) or after (retrospective study)?	
Test methods	7	The reference standard and its rationale	
	8	Technical specifications of material and methods involved including how and when measurements were taken, and/or cite references for index tests and reference standard	
	9	Definition of and rationale for the units, cutoffs, and/or categories of the results of the index tests and the reference standard	
	10	The number, training, and expertise of the persons executing and reading the index tests and the reference standard	
	11	Whether or not the readers of the index tests and reference standard were blind (masked) to the results of the other test and describe any other clinical information available to the readers	
Statistical methods	12	Methods for calculating or comparing measures of diagnostic accuracy, and the statistical methods used to quantify uncertainty (e.g., 95% confidence intervals)	
	13	Methods for calculating test reproducibility, if done	
RESULTS		Report	
Participants	14	When study was done, including beginning and ending dates of recruitment	
	15	Clinical and demographic characteristics of the study population (e.g., age, sex, spectrum of presenting symptoms, comorbidity, current treatments, recruitment centers)	
	16	The number of participants satisfying the criteria for inclusion that did or did not undergo the index tests and/or the reference standard; describe why participants failed to receive either test (a flow diagram is strongly recommended)	
Test results	17	Time interval from the index tests to the reference standard, and any treatment administered between	
	18	Distribution of severity of disease (define criteria) in those with the target condition; other diagnoses in participants without the target condition	
	19	A cross tabulation of the results of the index tests (including indeterminate and missing results) by the results of the reference standard; for continuous results, the distribution of the test results by the results of the reference standard	
	20	Any adverse events from performing the index tests or the reference standard.	
Estimates	21	Estimates of diagnostic accuracy and measures of statistical uncertainty (e.g., 95% confidence intervals)	
	22	How indeterminate results, missing responses, and outliers of the index tests were handled	
	23	Estimates of variability of diagnostic accuracy between subgroups of participants, readers, or centers, if done	
	24	Estimates of test reproducibility, if done	
DISCUSSION	25	Discuss the clinical applicability of the study findings	

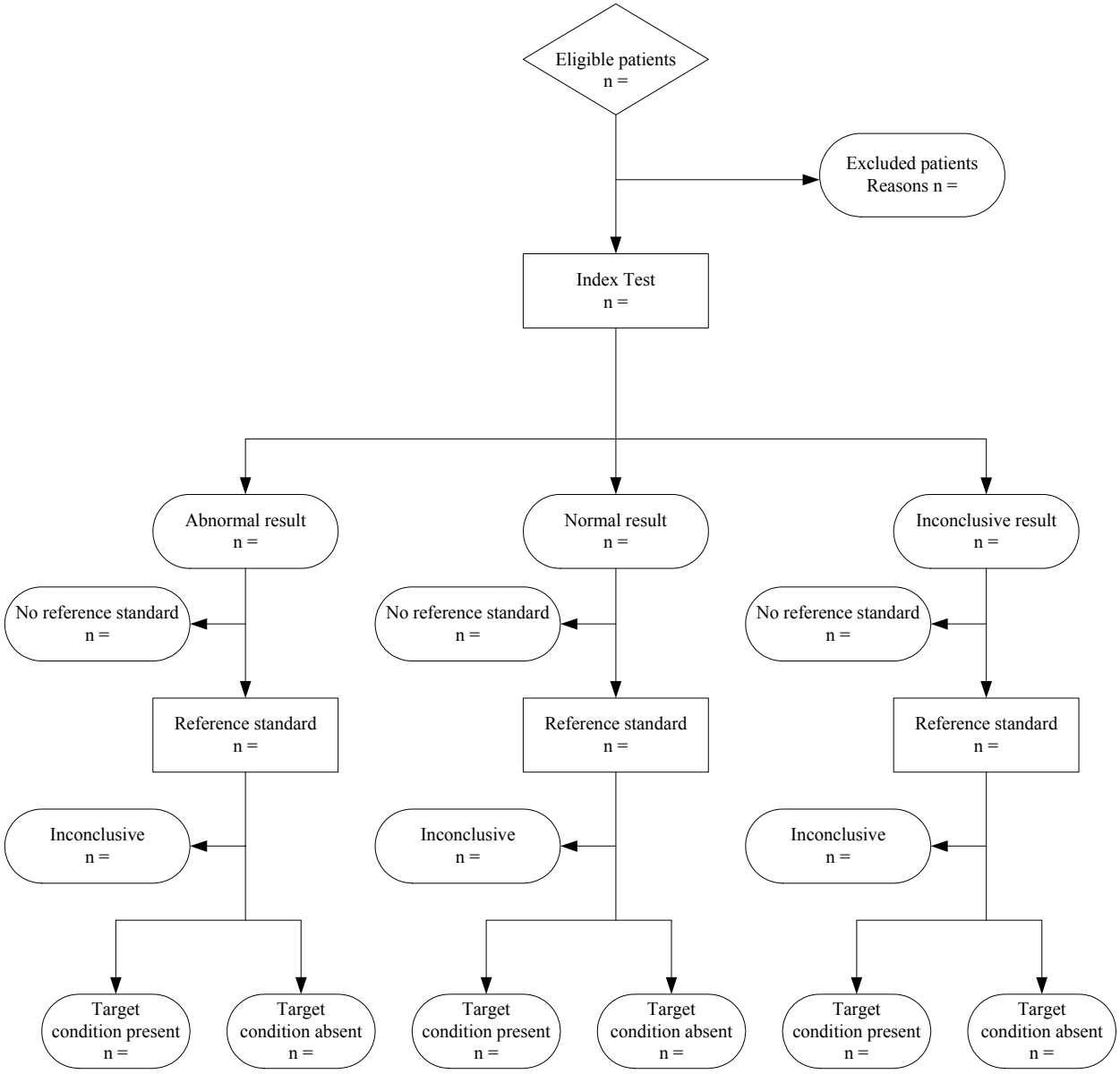

Figure 7. Template Diagram for Selection, Enrollment, and Follow-up of Study Subjects in a Diagnostic Accuracy Study. (From Bossuyt PM, Reitsma JB, Bruns DE, et al. Towards complete and accurate reporting of studies of diagnostic accuracy: The STARD initiative. Standards for Reporting of Diagnostic Accuracy. *Clin Chem*. 2003;49:1-6. Reprinted with permission from the American Association for Clinical Chemistry.)

7.3 Reporting Trials

Investigators should follow the recommendations of the Consolidated Standards for Reporting Trials (the CONSORT statement; see Table 13 and Figure 8) for reporting the results of randomized trials and follow the relevant sections for reporting the results of other study designs.

Table 13. CONSORT Checklist of Items to Include in Reporting a Randomized Trial. (From Altman DG, Schulz KF, Moher D, et al. The revised CONSORT statement for reporting randomized trials: Explanation and elaboration. *Ann Intern Med.* 2001;134:663-694. Reprinted with permission from the American College of Physicians.)

Paper Section and Topic	Item #	Descriptor	Reported on page #
Title and Abstract	1	How participants were allocated to interventions (e.g., "random allocation," "randomized," or "randomly assigned")	
Introduction			
Background	2	Scientific background and explanation of rationale.	
Methods			
Participants	3	Eligibility criteria for participants and the settings and locations where the data were collected	
Interventions	4	Precise details of the interventions intended for each group and how and when they were actually administered	
Objectives	5	Specific objectives and hypotheses	
Outcomes	6	Clearly defined primary and secondary outcomes measures and, when applicable, and methods used to enhance the quality of measurements (e.g., multiple observations, training of assessors)	
Sample size	7	How sample size was determined and, when applicable, explanation of any interim analyses and stopping rules	
Randomization	8	Method used to generate the random allocation sequence, including details of any restriction (e.g., blocking, stratification)	
Sequence generation			
Allocation concealment	9	Method used to implement the random allocation sequence (e.g., numbered containers or central telephone), clarifying whether the sequence was concealed until interventions were assigned	
Implementation	10	Who generated the allocation sequence, who enrolled participants, and who assigned participants to their groups	
Blinding (masking)	11	Whether or not participants, those administering the interventions, and those assessing the outcomes were blinded to group assignment. If done, how the success of blinding was evaluated.	
Statistical methods	12	Statistical methods used to compare groups for primary outcome(s); methods for additional analyses, such as subgroup analyses and adjusted analyses	
Results			
Participant flow	13	Flow of participants through each stage (a diagram is strongly recommended). Specifically, for each group report the numbers of participants randomly assigned, receiving intended treatment, completing the study protocol, and analyzed for the primary outcome. Describe protocol deviations from study as planned, together with reasons.	
Recruitment	14	Dates defining the periods of recruitment and follow-up	
Baseline data	15	Baseline demographic and clinical characteristics of each group	
Numbers analyzed	16	Number of participants (denominator) in each group included in each analysis and whether the analysis was by "intention to treat." State the results in absolute numbers when feasible (e.g., 10 of 20, not 50%).	
Outcomes and Estimation	17	For each primary and secondary outcome, a summary of results for each group and the estimated effect size and its precision (e.g., 95% confidence interval)	
Ancillary analyses	18	Address multiplicity by reporting any other analyses performed, including subgroup analyses and adjusted analyses, indicating those prespecified and those exploratory.	
Adverse events	19	All important adverse events or side effects in each intervention group	
Discussion			
Interpretation	20	Interpretation of the results, taking into account study hypotheses, sources of potential bias or imprecision, and the dangers associated with multiplicity of analyses and outcomes	
Generalizability	21	Generalizability (external validity) of the trial findings	
Overall evidence	22	General interpretation of the results in the context of current evidence	

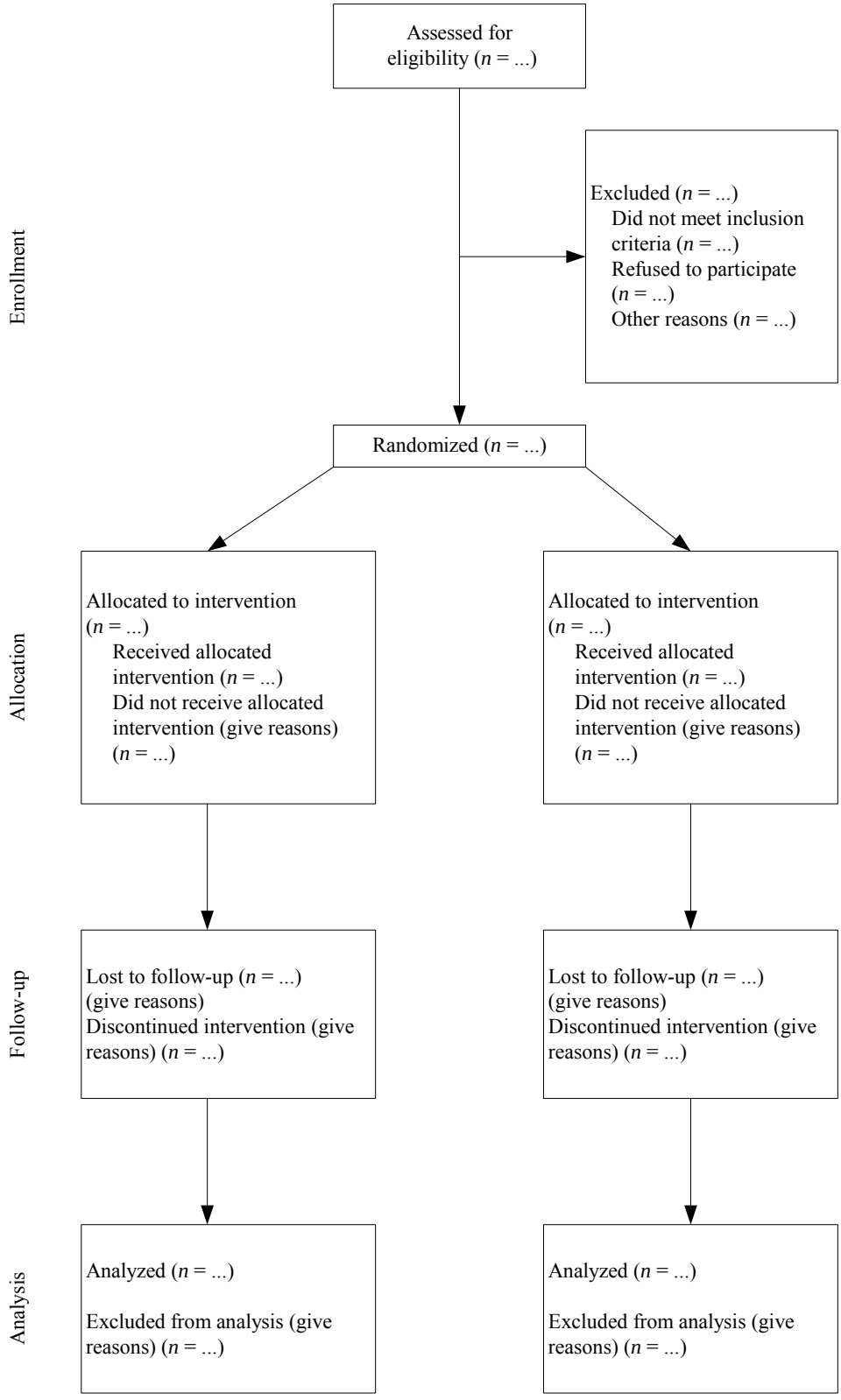

Figure 8. CONSORT Template Diagram for Selection, Enrollment, and Follow-up of Study Subjects in a Randomized Trial. (From Altman DG, Schulz KF, Moher D, et al. The revised CONSORT statement for reporting randomized trials: explanation and elaboration. *Ann Intern Med.* 2001:134:663-694. Reprinted with permission from the American College of Physicians.)

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Academy Health Glossary of Terms Commonly Used in Health Care	http://www.academyhealth.org/publications/glossary.htm
Agency for Healthcare Research and Quality (AHRQ)	http://www.ahrq.gov/
American Academy of Family Physicians (AAFP)	http://www.aafp.org/
American Association for Clinical Chemistry (AACC)	http://www.aacc.org/
American Association for Respiratory Care (AARC)	http://www.aarc.org/
American College of Medical Genetics (ACMG)	http://www.acmg.net/
American College of Physicians (ACP)	http://www.acponline.org/
American College of Physicians Compendium of Primers	http://www.acponline.org/journals/ecp/primers/ecp.primers.pdf
American Hospital Association (AHA)	http://www.aha.org/
American Medical Association (AMA)	http://www.ama-assn.org/
American Nurses Association (ANA)	http://www.ana.org/
American Public Health Association (APHA)	http://www.apha.org/
American Society for Clinical Laboratory Science (ASCLS)	http://www.ascls.org/
American Society for Clinical Pathology (ASCP)	http://www.ascp.org/
American Society for Microbiology (ASM)	http://www.asm.org/
American Osteopathic Association (AOA)	http://www.aoa-net.org/
Centers for Disease Control and Prevention (CDC)	http://www.cdc.gov/
Center for Medicare & Medicaid Services (CMS)	http://www.cms.hhs.gov/
CLMA	http://www.clma.org/
College of American Pathologists (CAP)	http://www.cap.org/
CONSORT Statement	http://www.consort-statement.org/
Food and Drug Administration (FDA)	http://www.fda.gov/
Health Resources and Services Administration (HRSA)	http://www.hrsa.gov/
Healthcare Information and Management Society (HIMSS)	http://www.himss.org/

International Federation of Clinical Chemistry and Laboratory Medicine (IFCC)	http://www.ifcc.org/
Japanese Society of Laboratory Medicine (JSLM)	http://www.jslm.org/english
Joint Commission on Accreditation of Healthcare Organizations (JCAHO)	http://www.jcaho.org/
National Academy of Clinical Biochemistry (NACB)	http://www.nacb.org/
National Institutes of Health (NIH)	http://www.nih.gov/
National Institutes of Health Guide for Grants and Contracts	http://grants.nih.gov/grants/guide/index.html
Uniform Requirements for Manuscripts Submitted to Biomedical Journals	http://www.icmje.org/

NCCLS consensus procedures include an appeals process that is described in detail in Section 8 of the Administrative Procedures. For further information, contact the Executive Offices or visit our website at www.nccls.org.

Summary of Delegate Comments and Subcommittee Responses

HS6-P: *Studies to Evaluate Patient Outcomes; Proposed Guideline*

General

1. A more clearly defined audience for the document with some tailoring of its content to meet their needs would be helpful. At present, someone with little or no research experience may find it unhelpful because it contains so much information and not enough specific directions on how to do research. On the other hand, someone more familiar with research may want further or more detailed information on some topics. If the different topics included sources of other information (e.g., texts, websites) in the body of the document, this would enable readers to easily find out more about a topic of interest.

- **The document is an NCCLS guideline developed through the NCCLS consensus process and describes general criteria for conducting studies of patient outcomes. It is not intended to be a primer or manual for conducting research. There are several excellent books available for readers interested in more specific information about how to conduct a patient outcomes study (see the Additional References section).**

  Several references have been added to the Additional References section including the following books: Aday LA, et al, *Evaluating the Medical Care System*; Bissell MG, *Laboratory-Related Measures of Patient Outcomes*; Hulley SB, et al, *Designing Clinical Research*; Mulrow C, et al, *Systematic Reviews*; Ogden TE, et al, *Research Proposals*; and Price and Christenson, *Evidence-Based Laboratory Medicine*.

  For readers interested in more specific information about how to design a patient outcomes research project, the text by Hulley would be an excellent first choice. For laboratorians, the book edited by Bissell, *Laboratory-Related Measures of Patient Outcomes: An Introduction,* and the book edited by Price and Christenson, *Evidence-Based Laboratory Medicine: From Principles to Outcomes,* are excellent introductions with an approach, terminology, and examples that are especially relevant to laboratory medicine. The texts by Aday, Crombie, Black, and Kane can provide valuable insight in thinking about patient outcomes research and methods of outcomes research. The books by Friedman and Fletcher are excellent introductions to the concepts of epidemiology and clinical epidemiology, and the text by Glantz is an excellent introduction to statistics for readers without a background in these areas. The texts by Friedman, Pocock, and Meinert provide more advanced and detailed information on design of randomized blinded clinical trials. Guyatt's anthology of articles from JAMA is an extremely helpful guide in understanding published patient outcomes research and related articles.

2. While there is discussion of the use of quantitative research methods, there is none about qualitative methods (e.g., data collection tools such as in-depth interviews, focus groups, and qualitative data analysis).

- **Qualitative research on patient outcomes addresses such topics as patients' experience of illness, patients' experiences in receiving healthcare services, and the attitudes and behaviors of clinicians and others in providing healthcare services. Qualitative research is inductive and aims to identify factors that may affect a patient's illness experience or experience in receiving health care. Qualitative research is especially important in generating coherent theories and hypotheses that can be subsequently tested using quantitative methods. Thus, qualitative research and quantitative research methods have a complementary role in patient outcomes research. Qualitative research uses "field observations" (direct observations of participants or indirect observation via audio or video recordings, interviews of individuals or groups, and analysis of a variety of types of documents to identify the context of a patient's illness experience and the patient's experience in receiving health care.**

The following articles have been added to the additional references section for users who are interested in obtaining additional information: Giacomini MK, Cook DJ. Users' guides to the medical literature: XXIII. Qualitative research in health care B. What are the results and how do they help me care for my patients? Evidence-Based Medicine Working Group. *JAMA*. 2000;284:478-482. Giacomini MK, Cook DJ. Users' guides to the medical literature: XXIII. Qualitative research in health care A. Are the results of the study valid? Evidence-Based Medicine Working Group. *JAMA*. 2000;284:357-362.)

3. The inclusion of a bibliography structured around different topics would be useful so that readers can more easily identify further sources of information that are of interest to them, e.g., designing research projects, developing data collection tools, data analysis.

- **The bibliography includes several texts that address a range of topics and a small number of references. The response to Comment 1 provides suggestions for further reading.**

4. The document would be strengthened through the inclusion of more laboratory-specific examples of the types of outcomes research that are relevant to NCCLS members.

- **In an earlier draft version of HS6, detailed examples of laboratory-specific study designs were included; however, in keeping with the mission of the Area Committee on Healthcare Services, the subcommittee prepared a guideline that would be useful across the entire healthcare field. Also, the material presented in the previous format was more appropriate for a primer or handbook rather than a guideline.**

  The following laboratory-specific examples are provided which illustrate the use of the variety of study designs that can be used in patient outcomes research.

  - **Survey: Peddecord KM, Baron EJ, Francis D, Drew JA. Quality perceptions of microbiology services. A survey of infectious diseases specialists. *Am J Clin Pathol*. 1996;105:58-64.**
  - **Cohort Study: Ridker PM, Glynn RJ, Hennekens CH. C-reactive protein adds to the predictive value of total and HDL cholesterol in determining risk of first myocardial infarction. *Circulation.* 1998;97:2007-2011.**
  - **Case-Control Study: Jacobsen SJ, Bergstralh EJ, Guess HA, et al. Predictive properties of serum-prostate-specific antigen testing in a community-based setting. *Arch Intern Med.* 1996;156:2462-2468.**
  - **Randomized Controlled Trials: Schein OD, Katz J, Bass EB, et al. The value of routine preoperative medical testing before cataract surgery. Study of Medical Testing for Cataract Surgery. *N Engl J Med.* 2000;342:168-175; and Mandel JS, Church TR, Bond JH, et al. The effect of fecal occult-blood screening on the incidence of colorectal cancer. *N Engl J Med.* 2000;343:1603-1607.**
  - **Nonrandomized Between-Group Study: Mancuso CA. Impact of New Guidelines of Physicians' Ordering of Preoperative Tests. *J Gen Intern Med.* 1999;14:166-172.**
  - **Systematic Review: van Walraven C, Naylor CD. Do we know what inappropriate laboratory utilization is? A systematic review of laboratory clinical audits. *JAMA*. 1998;280:550-558.**
  - **Cost-Effectiveness Analysis: CDC Diabetes Cost-Effectiveness Study Group. The cost-effectiveness of screening for type 2 diabetes. CDC Diabetes Cost-Effectiveness Study Group, Centers for Disease Control and Prevention. *JAMA*. 1998;280:1757-1763.**

5. For the novice, reading and implementing the information in this document will be difficult without other text and/or consultative support.

- **Specific suggestions (see responses to Comments 1 and 4 above), additional references (see Additional References section), and examples cited in the text are provided to assist novice readers in learning more about patient outcomes studies and health services research methods.**

6. The document would be strengthened with the addition of more laboratory-specific examples of the types of outcome research that are relevant to NCCLS members.

- **See response to Comment 4, above.**

7. I expected to see more of an emphasis on studies of the type that examine the relationship of an intervention to subsequent patient outcomes (and to costs of care). It does not seem realistic to also address other areas in this

guideline. There is a clear need for an entire separate guideline on the conduct of studies of diagnostic accuracy. The conduct and reporting of these studies remain poor. (See Bossuyt PM. The quality of reporting in diagnostic test research: getting better, still not optimal. Clin Chem. 2004 Mar;50(3):465-6.) In my experience, few authors of papers understand the principles of diagnostic test research well enough to follow the STARD checklist. The need for a separate document on studies of diagnostic accuracy is reinforced by the fact that studies of diagnostic accuracy of tests are common, whereas studies of the impact of diagnostic testing on outcomes remain rare.

- **Laboratory tests, imaging tests, and other types of diagnostic tests may have a direct impact on the process of care and a less direct impact on patient outcomes. Users may consult the following for additional information: Silverstein MD, Laboratory Services, A Health Services Research Perspective, Chapter 2 in Bissell (editor), *Laboratory-Related Measures of Patient Outcomes*; Kling E, Hess JR, The Relationship Between Test and Outcome in Price and Christenson, *Evidence-based Laboratory Medicine*. An example of an approach to patient outcomes using a conceptual framework to identify measures related to outcomes can be found in Silverstein MD, Laboratory Tests for Case-finding and Screening in the Ambulatory Setting, Chapter 9 in Bissell (editor) *Laboratory-Related Measures of Patient Outcomes.***

  The subcommittee agrees that a separate guideline focused on studies of diagnostic accuracy may also be useful.

8. For an NCCLS guideline, there would be merit in addressing in detail some of the unique challenges of outcomes studies of diagnostic interventions, such as the usual need to tie some action (usually therapeutic) to the result of the diagnostic test in order to see an effect on outcomes. The authors of this NCCLS guideline are knowledgeable about such issues and are well positioned to address them.

- **The subcommittee agrees. References cited above address these issues. Interested users should review the following for additional information: St John and Price, Measures of Outcome, Chapter 4 in Price and Christenson, *Evidence-based Laboratory Medicine;* Fryback DG, Thornbury JR. The efficacy of diagnostic imaging. *Med Decis Making*. 1991;11:88-94; and Silverstein MD, Boland BJ. Conceptual framework for evaluating laboratory tests: case-finding in ambulatory patients. *Clin Chem*. 1994; 40:1621-1627.**

9. There would be merit in including citations of recent relevant papers on outcomes research related to diagnostic testing and some discussion of such papers. I would particularly recommend some discussion of a paper by Bossuyt, Lijmer and Mol, Randomized comparisons of medical tests: sometimes invalid, not always efficient. Lancet. 2000 Nov 25;356(9244):1844-7. An abstract of another paper from that group is attached. The recent AACC book edited by Chris Price and Rob Christenson contains several relevant chapters.

- **The citation has been included as recommended.**

10. Examples of primary studies would also be welcome. Examples might include Schein OD et al. The value of routine preoperative medical testing before cataract surgery. Study of Medical Testing for Cataract Surgery. N Engl J Med. 2000 Jan 20;342(3):168-75 and Mandel et al. The effect of fecal occult-blood screening on the incidence of colorectal cancer. N Engl J Med. 2000 Nov 30;343(22):1603-7.

- **The subcommittee agrees. See response to Comment 4, above.**

11. A cautionary note should be included to emphasize that legislative requirements may vary internationally, and users should ascertain information on jurisdiction.

- **Section 5.5.2 has been revised to include warnings to investigators to assure adherence to all applicable laws, rules, regulations, and policies.**

<u>Title</u>

12. The title seems a bit misleading as the document is broad and addresses not only the type of studies that the clinical laboratory literature calls "outcomes studies," but also addresses such things as studies of diagnostic accuracy of tests. The document might almost be called an introduction to clinical epidemiology. Is there a

need for a document to do that and to define terms that will be used in other NCCLS documents? If so, it is virtually in hand.

- **The subcommittee agrees that the document could be used for a variety of purposes including those to evaluate diagnostic accuracy; therefore, terms have been defined in a manner that supports their use as basic vocabulary for other NCCLS documents. The subcommittee believes this is the strength of the current guideline.**

Foreword

13. The first sentence of the third paragraph should read, "…increasingly concerned…"

- **This typographical error has been corrected.**

Key Words

14. Did you intend to separate cost and effectiveness by a comma?

- **It was the intent of the subcommittee to list the terms as separate "key words."**

Section 2.1, Potential Impact of Outcomes Studies

15. First bullet: Interesting statistic presented. Is there a reference? It could be misleading since it does not distinguish between cleared and non-cleared (FDA), registered and non-registered products and procedures. Could look like the agencies are doing their job.

- **The subcommittee is uncertain of the distribution of products that are not reviewed by the FDA; therefore, the reference has been deleted.**

Section 3, Definitions

16. As with any consensus document, the writing can be a bit inconsistent. This is especially true for the examples or notes. For instance, compare the notes for the term "confounding" with the notes for "relative risk." Some are much easier to understand than others.

- **The notes provide supplementary information on the use of terms by different disciplines, such as epidemiology, demography, statistics, health services research, and health economics.**

  The notes for relative risk have been revised.

17. Modify the definition of "beneficence" to read, "The duty to do good *and avoid* harm to others."

- **The definition has been modified.**

18. In the definition for blinding//masking, doesn't NOTE b refer to "triple blinding" (i.e., participants, caregivers, and those assessing outcomes)?

- **The definition has been revised.**

19. Modify the definition of "charges" to read, "…which may or may not be *proportional*…"

- **The definition has been modified.**

20. Modify definition of "cost" to read, "…the price of a service or amount billed an individual or third party, may or may not be equal *or even proportional* to service costs."

- **The definition has been modified.**

21. In the definition for "systematic review," the notes state that it differs from narrative reviews in several ways. Unfortunately, there is no definition for "narrative review." Consider adding a definition for this term.

- **The definition of systematic review has been revised to indicate the general characteristics of systematic reviews in contrast to other (usually older) styles of reviews. Systematic reviews have a more focused question, explicit protocol, with criteria for searching and appraising the literature identified. Systematic reviews are a subset of all reviews. Narrative reviews generally refer to those reviews that are not "systematic reviews."**

22. Type I error as defined ("false negative" or "alpha error") does not coincide with the term as discussed in Section 5.2.4 on Errors in Inference, in the second paragraph, in which it is referred to as a "false positive" or "alpha error."

- **The definition has been corrected.**

23. Definitions for both "Type I error" and "Type II error" state that these errors are "false negatives." The Type I error should state that it is a "false positive."

- **The definition has been corrected.**

24. The definitions section did not have RCT. It needs to be added to the randomized blinded trial because RCT is used in several other places in the document.

- **Randomized trials in clinical settings are often referred to as randomized clinical trials (RCTs). This term is often assumed to include blinding, since most (but not all) clinical trials use blinding to reduce bias. Randomization is a powerful method to reduce confounding. Randomization with blinding is even more powerful because it reduces bias. Randomization without blinding may be insufficient to prevent bias. Accordingly, randomized blinded trial (RBT) is recommended because it emphasizes the importance of methods to address both confounding and bias.**

  This information has been incorporated in Section 6.3.1. "RCT" has been changed to "RBT" for clarification.

Section 4.1, Essential Features of Outcomes Studies

25. Modify the second sentence of the first bullet as follows, "These outcomes include symptoms and signs of disease; results of laboratory tests…"

- **The text has been modified.**

Section 4.3, The Cycle of Outcomes Research

26. In Table 1 under "Conducting the Study," modify the sixth bullet to read, "Apply intervention if an interventional study design."

- **The text has been modified.**

Section 5.2.2, Testing Hypotheses

27. Modify the sixth line to read, "…allows the calculation of the probability (a "P-value") that the findings in the study occurred by chance" (i.e., delete parenthetical statement since it is not for exact p-values).

- **The text has been modified.**

Section 5.2.3, Estimating the Magnitude of Effects of Factors on Outcomes

28. In the last sentence, I suggest taking the 95% out. Change sentence to "This range may be expressed in percent as a confidence interval." Since there are no equations in this document...and 95% is a common confidence

interval, an unfamiliar reader may assume all data has a 95% confidence interval. I noted that in the definitions the 95% is used as an example. In that context it is appropriate.

- **The sentence has been revised and a phrase added to indicate that most often, a 95% confidence interval is reported.**

Section 5.5.2, Regulations and Laws Regarding Human Subjects Research

29. Regarding "individually identifiable health information," some expansion would be very valuable for individuals performing studies on diagnostic tests.

- **In the U.S., legislation was adopted which established regulations and procedures to assure protection of confidential patient data and privacy of patients (the Health Insurance Portability and Accountability Act or "HIPAA"). Individually identifiable health information includes name, address, numerical identification numbers, etc., which could be used to identify individual patients.**

Section 5.5.4, Investigator Responsibilities

30. Reword the third paragraph (beginning with the fifth line) as follows: "All authors must be willing to take responsibility for the research, *or for the parts (e.g., statistical analysis) under their control and at least one author must take responsibility for the research. All must* give final approval of the manuscripts submitted for publication. *To take responsibility and be accountable, authors must have access to the data*."

- **The text has been modified to read, "All authors must be willing to take responsibility for the research or for the portions under their control. At least one author must take responsibility for the entire research project. All authors must give final approval of manuscripts submitted for publication, and all authors must have access to the data."**

Section 6.1, Overview of Designs

31. In Table 3 under limitations (regarding the third bullet), is the limited power to study rare risk factors or rare outcomes in surveys and cohort studies worse than for interventional studies?

- **Observational studies such as surveys generally involve sampling of target population to make inferences about the target population. Rare risk factors may not be present in sufficient numbers to make precise estimates of proportion or have high statistical power to test for associations between groups. Cohort studies require observation of persons over time, and rare outcomes may not provide an adequate number of events to make precise estimates of rates or have high statistical power to test for associations between rare outcomes in persons with an exposure to a risk factor and persons without the exposure to the risk factors. The eligibility criteria of observational studies could be modified to ensure that a large enough sample of persons with rare risk factors is studied or a large size cohort is followed for a long enough time to ensure that an adequate number of events may occur to test the study hypotheses.**

  In contrast to observational studies, the risk and expense of interventional studies usually results in more selective screening of study subjects to minimize risk and focus resources on the smallest number of study subjects needed who meet study criteria. Thus, more often interventional studies are designed to study patients with rare risk factors by selectively enrolling study subjects with risk factors of interest or study patients at higher than average risk of conditions that are rare (have a low risk) in the general populations.

  Thus, the limitations are most often the result of practical aspects in conducting such studies, rather than inherent in the study design *per se*.

Section 6.2.3, Cohort Study

32. Consider citing an example in the last sentence of the paragraph. A good example of complexity of designs for outcomes studies of diagnostic testing is referenced in Bossuyt, Lijmer in Lancet 1999.

- **For each study design, substantial literature could be cited. Examples have been cited related to laboratory medicine in the response to Comment 4.**

Section 6.2.7, Types of Data (Now Section 6.7.1)

33. "Blood sugar" is a lay term. We recommend use of the scientific term, "blood glucose."

- **The text has been modified.**

Section 6.5.1, Common Study Questions and Study Designs

34. The third paragraph is unclear.

- **The paragraph has been revised for clarity.**

35. Insert the term "diagnostic" before the terms "accuracy," "sensitivity," and "specificity" in the sixth line of the first paragraph.

- **The text has been modified.**

36. In the fifth sentence of the third paragraph, "prognosis or outcomes" is unclear.

- **The text has been modified for clarification.**

37. Provide examples relevant to laboratorians

- **See examples in response to Comment 4.**

38. In Table 7, under the type of study therapy, the suggested design is Randomized Blinded Trial, which in Section 6.5.2 becomes randomized blinded trial (RBT). Is this a typographical error?

- **The text has been corrected.**

Section 6.6.4, Estimating the Number of Study Subjects Needed

39. In Table 9 under study design, the example is RCT of surgical or medical therapy. In Section 6.9.1, RCT is mentioned again. Is this another type of study or a typographical error (i.e., RBT)?

- **The text has been changed to reflect the correct term—a randomized blinded trial (RBT).**

40. Avoid the use of ± in Table 9 (i.e., untreated systolic BP between 140 and 150).

- **The text has been modified for clarity.**

Section 6.7.1, Types of Data

41. Replace the term "blood sugar" with "plasma glucose concentration."

- **The text has been modified.**

Section 6.7.3, Outcome Domains

42. Health-related quality of life measures (e.g., the SF-36) are recommended as reliable, valid, and responsive tools with no criticism of them (i.e., limitations).

- **The following references have been added to guide the reader to sources describing the strengths and limitations of these measures.**

- **The books by Aday, Black, Crombie, and Kane address outcome domains and outcome measurements.**

The following references may also be of use:

- **McDowell I, Newell C. *Measuring Health: A Guide to Rating Scales and Questionnaires*. New York: Oxford University Press; 1987.**
- **Cartwright A. *Health surveys in practice and potential: a critical review of their scope and methods*. London: King's Fund Publishing Office; 1983.**
- **Delamothe T. *Outcomes into Clinical Practice*. London: BMJ Publishing Group; 1994.**
- **Patrick DL, Erickson P. *Health Status and Health Policy: Quality of Life in Health Care Evaluation and Resource Allocation*. New York: Oxford University Press; 1993.**
- **Spilker B. *Quality of Life Assessments in Clinical Trials*. New York: Raven Press; 1990.**
- **Stewart AL, Ware JE, Jr. *Measuring Functioning and Wellbeing: The Medical Outcomes Approach*. Durham: Duke University Press; 1992.**
- **Streiner DL, Norman GR. *Health Measurement Scales*. Oxford: Oxford University Press; 1989.**
- **Wilkin D, Hallam L, Doggett M-A. *Measures of Need and Outcome for Primary Care*. Oxford: Oxford University Press; 1992.**

43. In Table 11, there are lines in Health-Related Quality of Life that should be removed.

- **The text has been corrected.**

Section 6.8, Interventions and Follow-Up

44. The concepts of "new pharmaceutical agents" in the second paragraph, and "broad class of interventions may include new clinical interventions such as drugs…" are confusing. Please clarify.

- **The text has been revised to clarify the intent of this phrase.**

45. In the last sentence of the third paragraph, replace the term "alternate" with "alternative."

- **The text has been corrected.**

46. Move the fifth paragraph on "Unit of Intervention" to become the fourth paragraph (i.e., following "Program or Policy Interventions").

- **The text has been modified as recommended.**

Section 7.1, Overview of Reporting

47. Add the following text after the second sentence of the first paragraph, "These publications must indicate the role or lack of a role of the study's sponsor(s) in (a) study design(s), data acquisition, data analysis (and interpretation), and the preparation of the report and the decision to publish the work."

- **This sentence has been added.**

Section 7.2, Reporting Studies of Diagnostic Accuracy

48. Explain why STARD is included in this section. It is not for studies to evaluate patient outcomes, is it?

- **While the STARD statement was not explicitly designed to be a set of standards for reporting of patient outcomes studies, STARD does provide a set of standards for reporting the results of studies of diagnostic accuracy and patient outcomes studies for patients who have received innovative diagnostic tests. The STARD statement also illustrates a set of standards analogous to the CONSORT statement for randomized blinded trials. Other efforts are underway to establish standards for reporting the findings from observational patient outcomes studies. Collectively these standards, along with this NCCLS guideline for patient outcomes studies, have great potential to improve the quality of patient outcomes**

research and facilitate the translation of the findings from patient outcomes research into policies and practices that improve patient outcomes.

References

49. Include the following references: Bossuyt PM, Lijmer J. Lancet; 1999 (on randomized trials), and Moher, David on CONSORT.

- **The following references have been added:**

  - **Bossuyt PM, Lijmer JG. Traditional health outcomes in the evaluation of diagnostic tests. *Acad Radiol.* 1999;6 Suppl 1:S77-80;discussion S83-4).**
  - **Bossuyt PM, Lijmer JG, Mol BW. Randomised comparisons of medical tests: sometimes invalid, not always efficient. *Lancet.* 2000;356:1844-1847.**

50. Include the website for *Clinical Chemistry* (www.clinchem.org) to reference 42.

- **Website information for organizations that might assist researchers has been added; however, website information for journals has not been included since this is not commonly accepted practice in publications.**

Additional References

51. Include Price and Christensen, AACC Press to the list of additional references under the heading of books.

- **This resource has been added.**

52. Include the CONSORT website (www.consort-statement.org) to the list of additional references under the heading of websites.

- **This resource has been added.**

The Quality System Approach

NCCLS subscribes to a quality system approach in the development of standards and guidelines, which facilitates project management; defines a document structure via a template; and provides a process to identify needed documents through a gap analysis. The approach is based on the model presented in the most current edition of NCCLS document HS1—*A Quality System Model for Health Care.* The quality system approach applies a core set of "quality system essentials (QSEs)," basic to any organization, to all operations in any healthcare service's path of workflow. The QSEs provide the framework for delivery of any type of product or service, serving as a manager's guide. The quality system essentials (QSEs) are:

Documents & Records	Equipment	Information Management	Process Improvement
Organization	Purchasing & Inventory	Occurrence Management	Service & Satisfaction
Personnel	Process Control	Assessment	Facilities & Safety

Path of Workflow

A path of workflow is the description of the necessary steps to deliver the particular product or service that the organization or entity provides. For example, GP26-A2 defines a clinical laboratory path of workflow which consists of three sequential processes: preanalytic, analytic, and postanalytic. All clinical laboratories follow these processes to deliver the laboratory's services, namely quality laboratory information.

HS6-A describes a path of workflow for evaluating patient outcomes. The steps included in the path of workflow are indicated by an "X."

Planning the Study															Conducting the Study										Reporting/ Disseminating the Study		
Formulate the research question	Assess feasibility	Assess scientific merit	Review literature	Assess relevance to practice	Develop specific aims and hypothesis	Select study design	Choose study setting and sites	Develop criteria for subject eligibility and exclusion	Plan analysis and sample size	Assess threats to validity (chance, bias, confounding)	Assess human subjects and ethical issues	Write protocol	Submit to institutional review committees	Obtain administrative approval	Secure funding	Assemble team	Train staff	Establish procedures and operations	Recruit subjects	Measure baseline characteristics	Apply intervention	Measure outcomes	Analyze results	Implement methods to reduce chance, bias, confounding	Interpret findings	Submit for publication	Report results to institution and funding agencies	Translate research into practice
X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Adapted from NCCLS document HS1—*A Quality System Model for Health Care*.

Related NCCLS Publication*

HS1-A **A Quality System Model for Health Care; Approved Guideline (2002**). This document provides a model for healthcare service providers that will assist with the implementation and maintenance of effective quality systems.

* Proposed- and tentative-level documents are being advanced through the NCCLS consensus process; therefore, readers should refer to the most recent editions.

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Community Hospital of the Monterey Peninsula (CA)
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Duke University Medical Center (NC)
Dwight David Eisenhower Army Medical Center (GA)
Eastern Health Pathology (Australia)
Emory University Hospital (GA)
Enzo Clinical Labs (NY)
Evangelical Community Hospital (PA)
Fairview-University Medical Center (MN)
Florida Hospital East Orlando
Focus Technologies (CA)
Focus Technologies (VA)
Foothills Hospital (Calgary, AB, Canada)
Franciscan Shared Laboratory (WI)
Fresno Community Hospital and Medical Center
Gamma Dynacare Medical Laboratories (Ontario, Canada)
Geisinger Medical Center (PA)
Guthrie Clinic Laboratories (PA)
Hagerstown Medical Laboratory (MD)
Harris Methodist Fort Worth (TX)
Hartford Hospital (CT)
Headwaters Health Authority (Alberta, Canada)
Health Network Lab (PA)
Health Partners Laboratories (VA)

Highlands Regional Medical Center (FL)
Hoag Memorial Hospital Presbyterian (CA)
Holy Cross Hospital (MD)
Hôpital du Sacré-Coeur de Montreal (Montreal, Quebec, Canada)
Hôpital Maisonneuve - Rosemont (Montreal, Canada)
Hôpital Saint-Luc (Montreal, Quebec, Canada)
Hospital Consolidated Laboratories (MI)
Hospital for Sick Children (Toronto, ON, Canada)
Hospital de Sousa Martins (Portugal)
Hotel Dieu Grace Hospital (Windsor, ON, Canada)
Huddinge University Hospital (Sweden)
Hunter Area Health Service (Australia)
Indiana University
Innova Fairfax Hospital (VA)
Institute of Medical and Veterinary Science (Australia)
International Health Management Associates, Inc. (IL)
Jackson Memorial Hospital (FL)
Jacobi Medical Center (NY)
John C. Lincoln Hospital (AZ)
Johns Hopkins Medical Institutions (MD)
Kadlec Medical Center (WA)
Kaiser Permanente (MD)
Kangnam St. Mary's Hospital (Korea)
Kantonsspital (Switzerland)
Kenora-Rainy River Regional Laboratory Program (Ontario, Canada)
Kimball Medical Center (NJ)
King Abdulaziz Medical City – Jeddah (Saudi Arabia)
King Faisal Specialist Hospital (Saudi Arabia)
LabCorp (NC)
Laboratoire de Santé Publique du Quebec (Canada)
Laboratorio Dr. Echevarne (Spain)
Laboratório Fleury S/C Ltda. (Brazil)
Laboratorio Manlab (Argentina)
Laboratory Corporation of America (NJ)
LAC and USC Healthcare Network (CA)
Lakeland Regional Medical Center (FL)
Landstuhl Regional Medical Center (APO AE)
LeBonheur Children's Medical Center (TN)
Lewis-Gale Medical Center (VA)
L'Hotel-Dieu de Quebec (Canada)
Libero Instituto Univ. Campus BioMedico (Italy)
Loma Linda Mercantile (CA)
Long Beach Memorial Medical Center (CA)
Louisiana State University Medical Center
Lourdes Hospital (KY)
Maimonides Medical Center (NY)
Marion County Health Department (IN)
Martin Luther King/Drew Medical Center (CA)
Massachusetts General Hospital (Microbiology Laboratory)
MDS Metro Laboratory Services (Burnaby, BC, Canada)
Medical College of Virginia Hospital
Medical University of South Carolina
Memorial Medical Center (Napoleon Avenue, New Orleans, LA)
Memorial Medical Center (Jefferson Davis Pkwy., New Orleans, LA)
Methodist Hospital (Houston, TX)
Methodist Hospital (San Antonio, TX)
Michigan Department of Community Health
Mid America Clinical Laboratories, LLC (IN)
Middlesex Hospital (CT)
Monmouth Medical Center (NJ)
Montreal Children's Hospital (Canada)
Montreal General Hospital (Canada)
National Serology Reference Laboratory (Australia)
NB Department of Health & Wellness (New Brunswick, Canada)
The Nebraska Medical Center
New Britain General Hospital (CT)
New England Fertility Institute (CT)
New England Medical Center (MA)
New York City Department of Health & Mental Hygiene
NorDx (ME)
North Carolina State Laboratory of Public Health
North Central Medical Center (TX)
North Shore - Long Island Jewish Health System Laboratories (NY)
North Shore University Hospital (NY)
Northwestern Memorial Hospital (IL)
Ochsner Clinic Foundation (LA)
O.L. Vrouwziekenhuis (Belgium)
Ordre professionnel des technologists médicaux du Québec
Orlando Regional Healthcare System (FL)
Ospedali Riuniti (Italy)
The Ottawa Hospital (Ottawa, ON, Canada)
OU Medical Center (OK)
Our Lady of the Resurrection Medical Center (IL)
Pathology and Cytology Laboratories, Inc. (KY)
Pathology Associates Medical Laboratories (WA)
Peking University Shenzhen Hospital (China)
The Permanente Medical Group (CA)
Piedmont Hospital (GA)
Pocono Medical Center (PA)
Providence Health Care (Vancouver, BC, Canada)
Provincial Laboratory for Public Health (Edmonton, AB, Canada)
Queen Elizabeth Hospital (Prince Edward Island, Canada)
Queensland Health Pathology Services (Australia)
Quest Diagnostics Incorporated (CA)
Quintiles Laboratories, Ltd. (GA)
Regions Hospital
Rex Healthcare (NC)
Rhode Island Department of Health Laboratories
Riverside Medical Center (IL)
Robert Wood Johnson University Hospital (NJ)
Royal Columbian Hospital (New Westminster, BC, Canada)
Sahlgrenska Universitetssjukhuset (Sweden)
St. Alexius Medical Center (ND)
St. Anthony Hospital (CO)
St. Anthony's Hospital (FL)
St. Barnabas Medical Center (NJ)
St. Christopher's Hospital for Children (PA)
St-Eustache Hospital (Quebec, Canada)
St. John Hospital and Medical Center (MI)
St. John's Hospital & Health Center (CA)
St. Joseph Mercy Hospital (MI)
St. Joseph's Hospital – Marshfield Clinic (WI)
St. Jude Children's Research Hospital (TN)
St. Mary of the Plains Hospital (TX)
St. Michael's Hospital (Toronto, ON, Canada)
Ste. Justine Hospital (Montreal, PQ, Canada)
Salem Clinic (OR)
San Francisco General Hospital (CA)
Santa Clara Valley Medical Center (CA)
Seoul Nat'l University Hospital (Korea)
Shands at the University of Florida
South Bend Medical Foundation (IN)
South Western Area Pathology Service (Australia)
Southern Maine Medical Center
Spartanburg Regional Medical Center (SC)
Specialty Laboratories, Inc. (CA)
State of Connecticut Dept. of Public Health
State of Washington Department of Health
Stony Brook University Hospital (NY)
Stormont-Vail Regional Medical Center (KS)
Sun Health-Boswell Hospital (AZ)
Sunnybrook Health Science Center (ON, Canada)
Sunrise Hospital and Medical Center (NV)
Swedish Medical Center - Providence Campus (WA)
Temple University Hospital (PA)
Tenet Odessa Regional Hospital (TX)
The Toledo Hospital (OH)
Touro Infirmary (LA)
Tripler Army Medical Center (HI)
Truman Medical Center (MO)
UCLA Medical Center (CA)
UCSF Medical Center (CA)
UNC Hospitals (NC)
Unidad de Patologia Clinica (Mexico)
Union Clinical Laboratory (Taiwan)
Universita Campus Bio-Medico (Italy)
University College Hospital (Galway, Ireland)
University of Alabama-Birmingham Hospital
University of Chicago Hospitals (IL)
University of Colorado Hospital
University of Debrecen Medical Health and Science Center (Hungary)
University of Illinois Medical Center
University of Maryland Medical System
University of the Ryukyus (Japan)
University of Wisconsin Hospital
The University of Texas Medical Branch
The University of the West Indies
University of Virginia Medical Center
University of Washington
USA MEDDAC-AK
US LABS, Inc. (CA)
UZ-KUL Medical Center (Belgium)
VA (Hampton) Medical Center (VA)
VA (Tuskegee) Medical Center (AL)
Valley Children's Hospital (CA)
Virginia Beach General Hospital (VA)
Virginia Department of Health
Virginia Regional Medical Center (MN)
ViroMed Laboratories (MN)
Washington Adventist Hospital (MD)
Washoe Medical Center Laboratory (NV)
Waterford Regional Hospital (Ireland)
Wellstar Health Systems (GA)
West Jefferson Medical Center (LA)
Wilford Hall Medical Center (TX)
William Beaumont Army Medical Center (TX)
William Beaumont Hospital (MI)
William Osler Health Centre (Brampton, ON, Canada)
Winn Army Community Hospital (GA)
Winnipeg Regional Health Authority (Winnipeg, Canada)
Wishard Memorial Hospital (IN)
Yonsei University College of Medicine (Korea)
York Hospital (PA)

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