

Tutorials in Clinical Research: Part III. Selecting a Research Approach to Best Answer a Clinical Question

J. Gail Neely, MD; James M. Hartman, MD; Mark S. Wallace, MD; James W. Forsen, Jr., MD

Objective: This is the third in a series of sequential "Tutorials in Clinical Research."^{1,2} The objectives of this specific report are to enable the reader to rapidly dissect a clinical question or article to efficiently determine what critical mass of information is required to answer the question and what study design is likely to produce the answer. **Study Design:** Tutorial. **Methods:** The authors met weekly for 3 months exploring clinical problems and systematically recording the logic and procedural pathways from multiple clinical questions to the selection of proper research approaches. The basic elements required to understand the processes of selection were catalogued and field tested, and a report was produced to define and explain these elements. **Results:** Fundamental to a research approach is the assembly of subjects and the allocation of exposures. An algorithm leading to the selection of an approach is presented. The report is organized into three parts. The tables serve as a rapid reference section. The initial two-part narrative explains the process of approach selection. The examples section illustrates the application of the selection algorithm. **Conclusions:** Selecting the proper research approach has six steps: the question, logic and ethics, identification of variables, data display considerations, original data source considerations, and selection of prototypical approaches for assembly of subjects. Field tests of this approach consistently demonstrated its utility. **Key Words:** Clinical research, tutorials, clinical trials, reviews.

Laryngoscope, 111:821-830, 2001

From the Clinical Research Working Group, Department of Otolaryngology—Head and Neck Surgery, Washington University School of Medicine, St. Louis, Missouri, U.S.A.

Drs. Neely, Piccirillo, and Lieu are previous Robert Wood Johnson Clinical Research Scholars, Yale University School of Medicine.

Editor's Note: This Manuscript was accepted for publication February 14, 2001.

Send Correspondence to J. Gail Neely, MD, Professor and Director, Otolaryngology, Neurotology, Base of Skull Surgery, and Director of Research, Department of Otolaryngology—Head and Neck Surgery, Washington University School of Medicine, 660 South Euclid Avenue, Box 8115, St. Louis, MO 63110, U.S.A.

INTRODUCTION

When practicing in a busy office, questions like these arise: What is the best treatment? What is the best way to rule out one of the diseases on the differential diagnostic list? What do I observe now that suggests the prognosis for this patient? My experience seems to be different from that just reported in a journal; if I look at my experience systematically, what would it really reveal?

The busy practitioner does not have time to waste. It would be helpful to know for what kind of study to search during a rapid literature review. For example, to determine the best treatment, a randomized, double-blinded, controlled clinical trial should be sought. To determine prognosis, a prospective cohort study should be sought.

Fundamental to the design of a research approach is the selection or assembly of subjects and how exposures or maneuvers are selected or observed. An algorithm for the selection of a research approach is given in Table I.

The purpose of this report is to assist the busy practitioner to define the clinical question in a researchable way and to rapidly determine the types of clinical research studies that are likely to yield valid information about the specific question. The report is organized into three parts; the first two parts describe and explain issues fundamental to understanding the selection process, first, parallels between clinical practice and clinical research and, second, definitions and descriptions of relevant basic information about research. The third part provides examples of the application of the algorithm in the review of articles and in preparing to do a study.

PARALLELS BETWEEN CLINICAL PRACTICE AND CLINICAL RESEARCH

Clinical practice to solve a medical problem and clinical research to answer a question are similar in that both are progressive. Each progressively builds to a final diagnosis or answer through a series of cumulative tests or projects.

For example, when a patient presents with a chief complaint (medical problem), the clinical practice ap-

TABLE I.
Algorithm for Selection of Prototypical Approaches for Assembly of Subjects.

1. Clinical problem/question
Medical model
2. Medical logic and ethics: purpose of the researchable question
Descriptive—indexes of spectrum
Comparative—indexes of contrast; indexes of association
Cause-effect (impact)—requires a control
Process—requires a criterion “gold” standard
3. Identification of variables
4. Data display and research logic: e.g., x-y plots, 2 × 2 tables, array of dimensional values, allocation of maneuver
5. Original data source
Recorded by protocol, yes/no
Research conducted prospectively in real time with concurrent original data recording (longitudinal)
Research conducted after original data set recorded (cross-section or as a surrogate for a longitudinal study)
6. Best selection from menu of prototypical approaches for assembly of subjects
7. New information from that study leading to new hypothesis/question

proach is to describe the symptoms and signs observed, formulate a hypothesis as to the differential diagnosis, and then systematically seek data to confirm or rule out each of the alternative diagnoses. Whenever possible and appropriate, one uses a criterion or “gold” standard, such as a biopsy, a surgical observation, or a sensitive and specific aggregate of test results, to confirm the diagnosis.

Sometimes this type of confirmation is not possible. In that case, the sum of the best available evidence from the patient and his or her clinical course is used as a surrogate to confirm the most probable diagnosis. This less rigidly confirmed diagnosis must be accepted with a healthy respect for the uncertainty of diagnostic error.

A physician who leaped from the chief complaint to the final diagnosis without an orderly and systematic search for supporting data would not be considered astute. Parenthetically, an applicant sitting for a board examination would be in serious trouble if he or she did the same.

A conceptually parallel view of clinical research can be made. Clinical research is also progressive, in that no single study is likely to answer the question completely. It usually takes several progressive studies to get the final answer.

For example, the general purpose of research is either descriptive (descriptive research) or comparative (comparative research). Comparative research is categorized into two types: cause-effect (impact) research and process research. All data require assurance that the method to acquire it is valid and reliable (process research). Comparative research seeks either to contrast variables or associate variables; each uses special statistical indexes of contrast or association to assess the comparisons.³

The criterion standard for confirmation in comparative clinical research is the double-blinded, controlled, randomized clinical trial. However, just like a biopsy or a surgical observation, the randomized experimental

method is not always appropriate. In that case, the physician must use other methods best suited to give valid information. As in the clinical arena, this requires the best possible surrogate methods, and the less rigidly confirmed answer to the question, again, must be accepted with a healthy respect for uncertainty.

Similar to the clinical arena, one would not consider the physician astute if he or she leaped from a descriptive study to conclusions about cause-effect impact.

To reiterate, research is progressive. One common error in reading and writing the literature is considering that one study must answer the question completely; it rarely does. A progressive research approach to answer a question over time is almost always required. In reading the literature, the accumulation of progressive, valid information leads to a better understanding of truth.

Identifying where we are in the pathway to answer the question and what research approach is required at each step is important in the rapid and efficient reading of the literature. Of course, if one seeks to personally conduct a clinical research project, choosing the proper research approach is an important first step.

Basic Information

The primary reason to better understand clinical research is to keep our clinical acumen sharp. Clinical experience is not only what one does, but also what one reads and assimilates; if poor information is assimilated into one’s experience, it begins to degrade the experience.

Original Data Source

The essence of research is data; this implies measurement. Cumulated data are often referred to as a data set or data source. Two fundamental and independent attributes differentiate data: first, the temporal relationship of original data collection to the initiation of the research project and, second, the methodological rigor with which the original data were collected.

Research may be conducted in real forward time, concurrent with the acquisition of the original data set, as in a prospective study. Conversely, it may be conducted after the original data set has been obtained, as in a retrospective study of medical records or a secondary data set. Secondary data analysis is the re-examination of some or all of the data that were previously collected for another purpose; these data are known as a secondary data set.^{4,5} See Table II for a partial list of secondary data sets.

The original data set may be recorded by a specific protocol, such as in a prospective study or tumor registry. Conversely, it may be recorded without a protocol, such as in the medical records of most clinical practices.

Every research project, even a retrospective study or critical review of the literature, should be conducted using a prospectively (a priori) designed protocol for the acquisition of data to be analyzed. However, medical records are often first reviewed to see what is there, before a protocol is designed to define what is to be extracted and how it will be recorded for analysis. An a priori designed study protocol does not imply that the original data set was obtained by protocol. For example, a prospectively designed

project to review medical records looks at nonprotocol recorded original data.

Because systematic and random biases are major problems in clinical research, research data acquired and analyzed with the greatest attention to detail for minimizing bias are most valid and reliable. Therefore, the most robust data are those in which the original information was prospectively recorded by protocol and in which the research was concurrently conducted forward in real time during the original data collection. Examples are the randomized clinical trial and the prospective cohort study; these approaches are the principal ones for confirmation testing of hypotheses.

However, just as some clinical questions may not be answerable with a biopsy or a surgical observation, randomized trials or prospective cohort studies may not be feasible or appropriate for some research questions. For example, a case-control study may be more appropriate to determine putative risk factors for low-prevalence diseases. If the original data on which such a retrospective study is based were obtained by protocol, it will be an even stronger study. Another example is a cross-sectional study, which is the specific study design to determine prevalence; again, if the original data set was recorded by a protocol, the study is stronger.

Much like in clinical practice, the decision as to the best research approach must be made on the basis of the problem, or question, and the design's ability to solve the problem or answer the question.

Practices that are organized with data entry forms, alias history and physical forms, follow-up forms, and surgical record forms, that all permit clinical data to be recorded by protocol are rich sources of clinical research data sets. There are great examples of these practices throughout the United States that the senior author has had the pleasure of seeing.

Variables

A variable is "a characteristic that can be manipulated or observed and that can take on different values, either quantitatively or qualitatively."⁵ By definition, variables vary; the values or levels are not constant. A characteristic becomes a variable by virtue of how it is used in a study. For example, if side, left or right, is an important characteristic in a study and can vary, "side" is a variable. On the other hand, if only the right side is being studied, "side" is not a variable because it does not vary.⁵

Variables may be classified as *independent*, also known as treatment or predictor, variables and *dependent*, also known as response or outcome, variables. An independent variable has levels; a dependent variable has values. A variable must be operationally defined; this means that the methods for measuring it must be clearly delineated.⁵

An independent variable is a manipulated variable, which is set by the researcher; the researcher controls the level or accepts nature's levels. For example, in an experimental study of treatment A versus treatment B, "treatment" is the independent variable with two levels, A and B; treatments A and B are not two independent variables,

TABLE II.
Secondary Datasets.⁴

Individual datasets (data on individual subjects)
<ul style="list-style-type: none"> ● State, city, county death certificates ● National death index ● National hospital discharge survey ● Computerized registries of hospital discharge data ● National Ambulatory Medical Care Survey ● Health and Nutrition Examination Survey (HANES) ● National health interview survey ● Tumor registries ● Social Security records ● Previous research studies (small and large cohorts like Framingham, MRFIT) ● Computerized records from hospitals and clinics ● Roswell Park Hospital data ● Mayo Clinic data for Olmsted County ● Third party databases (Medicare, Medicaid, private insurance companies, Workmen's Compensation, HMOs) ● Trade union and company records ● Military data
Aggregate datasets (no individual data, but group data)
<ul style="list-style-type: none"> ● Local, state, national, international vital statistics ● United Nations demographics yearbook ● United Nations statistical yearbook ● Statistical Abstract of Latin America ● Statistical Abstract of the United States ● Vital Statistics of the United States ● Reportable disease registries ● Census

but two levels of one variable. In statistics, independent variables are designated as "X." A dependent variable is an observed variable, usually set by nature. In statistics, it is designated as "Y."⁵

Whether a variable is independent or dependent is also a function of how it is used in the study. For example, "outcome" would be a dependent variable in a clinical trial testing the independent variable "treatment" in this study that looks forward. Conversely, "outcome" would be the selected, independent variable in a case-control study to determine whether treatment made the difference and "treatment" would be the observed, dependent variable in this study that looks backward.

Research assumptions suggest that the dependent variable is caused by or is associated with the independent variable,⁵ that is, $Y = f(X)$; in other words, Y is a function of X.

General Research Outline Structure and Direction

The general structure for research is outlined as moving forward in real time from left to right and has the following basic components:

BASELINE --- MANEUVER --- OUTCOME

The temporal direction of the research examination of the data may be forward, from left to right in real time,

such as in clinical trials or cohort studies; backward, from right to left, such as in case-control studies; or concurrent, looking at all elements at the same time to determine events like prevalence, such as in cross-sectional studies.³

Each element of the outline has variables; some of these may be important to the question and are selected for study. The selected variables are then examined to determine their descriptive spectrum characteristics, contrasts, or associations: "Research is performed to examine the relationship among variables."⁵

Medical Outline Structure and Direction

In medical practice, events occur chronologically in real time and are often displayed in English writing from left to right. If one were going to outline a model of medical practice in the same format as the general research outline mentioned above, it would have the following form as it temporally progresses from left to right:

PREDISEASE STATE -- EXPOSURE -- DISEASE -- MANEUVER -- OUTCOME

In the predisease state, the patient is exposed to risk factors or agents that may cause disease or is exposed to preventive maneuvers that hope to prevent disease. *Risk factors* refer to the risk of getting the disease, as opposed to *prognostic factors*, which relate to the outcome after disease.

Once disease has occurred or is suspected, procedures are employed to detect the presence or absence of disease and therapeutic maneuvers are used to improve the outcome otherwise destined to occur if the disease is unchecked.

Prognostic factors, in addition to maneuvers, may intervene to influence outcome. Some of these factors might exist in the predisease state; others may surface only when the disease is manifest. For example, in a patient with cancer, age or pre-existing comorbidity in the precancerous period may influence the ultimate outcome; the stage of the cancer, which does not surface until the cancer is diagnosed, may also influence the outcome.

Table III shows the types of clinical questions that arise in daily practice and where they fit in the medical outline model.

The tripartite structure of the research outline often divides the medical model into two parts. "Baseline" refers to the starting point, usually the predisease state, or the disease state. "Maneuver" refers to agents capable of effecting change, such as exposure to risk factors, therapeutic or preventative interventions, or diagnostic procedures. "Outcome" refers to the response after the maneuver, as the disease or as the outcome.

However, variables of interest may be pulled from any or all of the temporal elements in the medical outline model. For example, as mentioned earlier in the discussion of prognostic factors, the study's dependent variable, outcome after intervention, may require assessment of independent variables in the predisease state, within the disease, and, as well, the usual independent variable, maneuver. See Table IV for examples of variables associated with the elements in the medical model.

Prototypical Research Designs and Purpose

The prototypical research designs, characterized by the particular assembly of subjects or the original data source, by what is to be ascertained, and by the direction of the research, are as follows: randomized clinical trials (basic design and variations), prospective cohort study (single and double), retrospective cohort study, nested case-control study within a cohort study, case-control study, and cross-sectional study⁶ (Table V).

There are many other structures for designs, including serial surveys and time series study, and special considerations are necessary for diagnostic and process research studies.^{3,5-9}

Diagnostic studies are best understood by constructing data for a 2 x 2 contingency table, discussed later in this report. Process research, such as test-retest reliability or intraobserver or interobserver variability, compares the performance of two or more maneuvers or procedures, not the change caused by them. For example, if a grading scale is to be tested to determine how reliably it performs when different observers use it, process research would compare the results of observer A using the scale on a series of subjects with that of observer B using the same scale on exactly the same subjects. The statistical tool

TABLE III.
Temporal Progression of Elements in Medical Model (1-5) and Types of Associated Clinical Questions.

1) Pre-Disease State	2) Exposure (or Maneuver)	3) Disease	4) Maneuver (or Procedure)	5) Outcome
Range of normal; spectrum of attribute variables; prevalence of attribute variables	Etiology; pathogenesis; prevention; risk factors; risk of disease	Natural history; spectrum of disease; prevalence; incidence	Treatment; safety; prognostic factors; prognosis; rehabilitation	Spectrum of outcomes; prevalence of outcomes
			Diagnosis -Screening (case finding) -Exclusion (differential diagnosis) -Confirmation (diagnosis) Intraobserver variability; interobserver variability; quality of care evaluation; quality of life evaluation	

TABLE IV.
Examples of Variables Associated With Elements in the Medical Model.

Pre-disease State	Exposure/Maneuver	Disease, Nosologic Categories	Maneuver/Process	Outcome
Age; gender; race; demographics; heredity; item of interest	Radiation; microorganisms; toxic agents; psychological stressors; preventions; genetic mutation	Traumatic; metabolic; medicinal/toxic; congenital/developmental; collagen/immunological/allergic; neoplastic/growths; infectious; degenerative/idiopathic; psychogenic	Treatments; rehabilitation; diagnostics	Recovery; adverse events; test results

would be looking at agreement, or concordance. The reader is encouraged to cross-reference Table I in the first report of this *Tutorial* series.¹

The purpose of the study focuses the research design selected. Studies have the following general purposes: descriptive or comparative. Even when first beginning to think about a study, the type of statistical indexes to assess the results must be considered, to properly design the study.*

Descriptive studies seek to describe and to determine the spectrum and frequency of the variables of interest.

Comparative studies seek to compare maneuvers by measuring the outcome from each. These studies require at least two maneuvers, the new or experimental maneuver (usually referred to as "A") and a comparative maneuver (usually referred to as "B").⁵ In cause-effect research, the comparative maneuver is the "control," which is either a placebo or a well-established standard of care. In process research, the comparative maneuver is a gold standard, more formally called a criterion standard.³

An example of a prototypical design is a randomized clinical trial. Herein, the purpose is to contrast maneuvers. Subjects with a specific disease for which the trial interventions make sense are assembled as a single group and then separated into two or more groups according to the random allocation of the treatment they are to receive. The treatment outcome would be identified as the dependent variable to be ascertained, and the direction of study would be forward.

Another example is the assembly of medical records, as the original data source, to be reviewed for a case-control study. In this type of study, medical records of "cases," those with the disease (outcomes from effects of risk factors), and suitable records for comparison of "controls," those without disease (comparative outcomes), would be assembled. The question is what seemed to cause the disease (i.e., risk factors); these might appear in the predisease state variables and in the agents to which the subjects may have been exposed. The focus of the study would be to ascertain these risk factor "exposures" and to determine whether the exposures differ significantly be-

tween the two groups. This is accomplished by estimating the strength of association between each putative risk factor and the outcome variable, the presence or absence of disease; this estimate is in the form of an "odds ratio," which will be discussed in a subsequent report.⁶ The direction of the study would be backward because presumably the exposures occurred before the disease, which is where this study began.

Variables Associated With Clinical Questions and Research Design

Variables of interest and their designation as independent (i.e., predictor) variables or dependent (i.e., outcome) variables may come from any or all of the temporal elements in the medical model. Table VI illustrates the medical model elements from which variables are chosen and the prototypical research design with which they are associated to answer clinically relevant questions.

Data Display and Research Logic

There are a number of data displays and logical concepts commonly encountered in clinical research that are helpful in visualizing how things fit together, especially when one is thinking of how to approach looking for the right information in the literature or designing a study. Here are a few that we have found helpful.

X-Y plots. When one variable is considered for association with another variable, an x-y plot is useful to diagram the possible relationships. For example, when vestibular Schwannoma tumor growth is considered, the x-axis is time and the y-axis is some measure of tumor expansion, such as a magnetic resonance imaging (MRI) scan. If some physiological change over time, say an audiometric parameter, is considered, again, the x-axis would be time and the y-axis would be the change in the physiological parameter. If an association between tumor growth and the physiological measure were to be the focus of the study, the x-axis could be the anatomical change and the y-axis could be the physiological change at the same time intervals. This simple x-y graphic illustration helps to demonstrate what the study may attempt.

Two-by-two contingency tables. Another example of a simple illustration to help picture what a study is attempting is a 2 × 2 contingency table (Table VII). Some authorities think that a 2 × 2 table can illustrate most research findings, at least for a better, abbreviated view of

*The reader is referred to Table I in Part I of this series (p. 1598), to review matching statistical tools with data types.¹ Descriptive statistics (indexes of spectrum) are used for descriptive research. Indexes of contrast are used for studies comparing the contrasts between groups. Indexes of association are used to assess the association between variables.³ Future articles will address the relevance of statistics to research design and analytical medical thinking.

TABLE V.
Prototypical Research Designs.

Assembly in Current Time	Future Time
	$\rightarrow \checkmark O$ $\rightarrow \checkmark O$
<p>1) Randomized Clinical Trial (RCT)—assemble subjects</p>	$\rightarrow \checkmark O$ $\rightarrow \checkmark O$ $\rightarrow \checkmark O$ $\rightarrow \checkmark O$
<p>2) Stratified RCT—assemble subjects</p>	$\rightarrow \checkmark O$ $\rightarrow \checkmark O$
<p>3) Prospective cohort, single, internal control—assemble subjects</p>	$\rightarrow \checkmark O$ $\rightarrow \checkmark O$
<p>4) Prospective cohort, double, external control—assemble subjects by risk factor or maneuver</p>	$\rightarrow \checkmark O$ $\rightarrow \checkmark O$
<p>5) Retrospective cohort—assemble previous original dataset by risk factor or maneuver after maneuvers and outcomes have occurred (similar to case-control, except assembled by maneuver, rather than outcome)</p>	$\rightarrow \checkmark O$ $\rightarrow \checkmark O$
<p>6) Nested case-control study within a cohort study—assemble previous or concurrent original data from a cohort study, by outcome or disease after maneuvers and outcomes have occurred</p>	$\rightarrow \checkmark O$ $\rightarrow \checkmark O$
<p>7) Case-control study—assemble subjects or previous original data by outcomes or disease, after maneuvers and outcomes have occurred</p>	$\rightarrow \checkmark O$ $\rightarrow \checkmark O$
<p>8) Cross-sectional study—assemble subjects or previous original data by variable of choice after maneuvers and outcomes have occurred</p>	$\rightarrow \checkmark O$ $\rightarrow \checkmark O$
<p>9) Prospective cohort for process research or a diagnostic study</p>	$\rightarrow \checkmark O$ $\rightarrow \checkmark O$

= Baseline state.

M = Maneuver, exposure, or procedure.

O = Outcome (outcome can be outcome after treatment of disease or disease after exposure to etiological factor).

⊗ = Randomization (same structure may be used for investigator selected maneuver, but by means other than by randomization).

X = Assembled by.

✓ = To be ascertained.

what is going on. Certainly, in diagnostic studies and process research, the contingency table is important.

Stem-and-leaf plots. For long arrays of dimensional data, a 2×2 table is often inadequate to picture what is

happening. Dimensional data are arrays of equal interval measurements, such as age, cubic centimeters of blood loss, or weight. These arrays are often compared by their means and the spread of the data about the mean.

Conceptually, it might be difficult to grasp what this data means if one is looking only at two rows of numbers. A characteristic way to look at this type of data is by using “bell” curves. Often, two curves are shown beside each other, with overlapping portions and the mean marked within the curve. By looking at two such curves, the distance between means can be seen and the effect of the spread of the data can be seen. A decision limen demarcating “positive” on one side and “negative” on the other side of the line can be drawn in different places, and the false-positive and false-negative rates, as well as positive predictive and negative predictive values, can be easily seen.

An easy way to graphically convert arrays of numbers into these curves is to construct them as frequency distribution histograms by a technique known as a “stem-and-leaf plot.”⁵ This method identifies the right most single digit as a “leaf” and the digits to the left of the leaf as the “stem.” The “stem” digits represent bins and the “leaves” represent the frequency count in the bin; in other words, the “leaf” numbers should be considered simply space holders in a bar graph, not numbers of meaning.

For example, if data were 10, 12, 20, 24, 26, 31, 32, 33, 34, 35, 43, 44, 49, 56, 59, and 125, the stem-and-leaf plot would look like this:

5														
4														
6	3	9												
2	4	2	4	9										
0	0	1	3	6									5	
1	2	3	4	5	6	7	8	9	10	11	12			

The skewed curve to the right can easily be seen in this demonstration with a range from 10 to 125, a median of 34, and a mean of 40.

Allocation of maneuvers. Knowing how the maneuver will be feasibly and ethically allocated is helpful to select the research design. The two methods of allocating the maneuver are as follows: experimental, meaning set by the investigator in either a random or nonrandom manner, and survey, meaning observed by the investigator. An example of an experimental design is the randomized clinical trial.

A nonrandom method of allocation during a clinical trial is “minimization,” in which successive treatments are assigned to minimize the differences between groups in the baseline attributes.³ In most other studies, the maneuver is surveyed and not set, per se, by the investigator. Even in double cohort prospective studies, wherein the groups are assembled by maneuver, the investigator did not allocate the maneuvers.

EXAMPLES: ALGORITHM FOR SELECTING A RESEARCH APPROACH

The algorithm for selecting a research approach is outlined in Table I.

TABLE VI.
Examples of Predictor and Outcome Variables Associated With Clinical Questions and Research Design.

Type of Clinical Question	Predictor Variable (Independent; levels set by or accepted by investigator)	Outcome Variable (Response, Dependent; measured to determine values)	Prototypical Research Design
Range of normal; spectrum of attribute variables; prevalence of attribute variables	Pre-disease state		Cross-sectional; descriptive (random sample of large, appropriate population)
Etiology, pathogenesis, risk factors; risk of disease (hypothesis generating)	Disease	Exposure	Case-control
Etiology, pathogenesis, risk factors; risk of disease (hypothesis generating)	Exposure	Disease	Retrospective; cohort
Etiology, pathogenesis, risk factors; risk of disease (hypothesis testing; confirming)	Exposure	Disease	Prospective cohort
Prevention	Maneuver	Disease	Randomized clinical trial
Natural history	Disease	Outcome	Prospective cohort, single; descriptive
Spectrum of disease (hypothesis generating); prevalence	Disease		Cross-sectional; descriptive (random sample of large, appropriate population)
Spectrum of disease (hypothesis testing; confirming); incidence	Pre-disease state	Disease	Prospective cohort, single; descriptive
Treatment; safety; rehabilitation	Maneuver	Outcome	Randomized clinical trial
Prognostic factors; prognosis (hypothesis generating)	Outcome	Pre-disease attributes, maneuver	Case-control
Prognostic factors; prognosis (hypothesis generating)	Pre-disease attributes, maneuver	Outcome	Retrospective cohort
Prognostic factors; prognosis (hypothesis testing; confirming)	Pre-disease attributes, maneuver	Outcome	Prospective cohort
Diagnostic test; marker studies; prognostic tests	Test result	Disease (determined by a "gold" standard)	Cross-sectional study of fully representative single group

The current literature offers examples of different approaches and ways to illustrate the algorithm.¹⁰⁻¹² The way we will proceed with the examples is to think about them before we read much further than the title. This is a good way to learn how to determine what we should expect from the article and to prepare to search the literature for answers.

Example 1

"Tumor growth and audiometric change in vestibular Schwannomas managed conservatively."¹⁰

1. Clinical problem or question. Before reading the article, the title suggests the clinical problem. What evidence do we have to tell us what imaging and audiometric parameters do over time and how do they relate to each other?

The medical model (Table III) suggests that the *Natural History* of the **Disease** and/or *Diagnostic Procedures* could be the focus of the clinical question(s).

2. Medical logic and ethics: purpose of the researchable question. Once the physician and the patient decided on the option to follow the tumor, it would be ethical to systematically perform an audiogram and MRI at regular intervals and plot what happens over time. This is standard practice if one plans to follow rather than treat

the tumor; the only difference would be the prospective protocol to record the data longitudinally as it occurs.

Another way to look at this would be to retrospectively look at data already recorded, without protocol, in the medical record. The prospective design and concurrent protocol-based data recording would be the stronger of the two designs.

The general purpose of the research would be longitudinally comparative. The objective would be to describe the change in MRI and the change in an audiometric parameter(s) over time and to compare the two to determine whether an association exists between the two measures; time is common to both.

3. Identification of variables. The independent, or predictor, variable would be time. The dependent, or outcome, variables would be the results of the MRI and the results of audiometry at each time interval.

4. Data display and research logic. Because the study would seek to compare two or more variables, the association indexes used would concentrate on trend. Therefore, three x-y plots might be imagined. One would be MRI results on the y-axis and time on the x-axis. The second would be the audiometric parameter results on the y-axis and time on the x-axis. The third would be the audiometric parameter results on the y-axis and the MRI image results on the x-axis.

TABLE VII.
2 × 2 Contingency Table.

	Disease or Outcome		
	Present or Success	Absent or Failure	
Test positive or experimental maneuver	a	b	a + b
Test negative or comparative maneuver	c	d	c + d
	a + c	b + d	a + b + c + d

a through d = numbers of subjects in each cell.

Rows = comparative tests or comparative maneuvers.

Columns = criterion standard "truth" for diagnostic or marker studies; outcome for comparative maneuvers.

a + b = number of subjects with positive test results or exposure to experimental maneuver.

c + d = number of subjects with negative test results or exposure to comparative maneuver.

a + c = number of subjects with disease or successfully treated.

b + d = number of subjects without disease or treatment failures.

a + b + c + d = number of total subjects in study.

For diagnostic or marker studies:

a = true positive.

b = false positive.

c = false negative.

d = true negative.

Sensitivity = given the disease is present (a + c), how sensitive is the test in detecting the disease (a); $a/a + c$.

Specificity = given no disease (b + d), how specific is the test in indicating no disease (d); $d/b + d$.

Positive Predictive Value = given the test is positive (a + b), how sure are we that the subject has the disease

(a); $a/a + b$.

Negative Predictive Value = given the test is negative (c + d), how sure are we that the subject does not have the disease (d); $d/c + d$.

Because both MRI and audiometry will be performed on all subjects, random allocation of a maneuver would not be appropriate; however, the investigator does allocate both maneuvers to all in a nonrandom manner.

5. Original data source. The best approach would be to conduct the research prospectively and look longitudinally forward, in real time, using concurrent protocol-driven data recording.

6. Best selection from menu of prototypical approaches for assembly of subjects. See Table V.

The choice "Prospective Cohort for Process Research or a Diagnostic Study" (Table V) would best fit the intent of the approach just analyzed.

The actual study reported was a prospective design and did assess the correlation (association) for trend. This is a good example of a well-conducted clinical study.

Example 2

"The health impact of chronic recurrent rhinosinusitis in children."¹¹

1. Clinical problem or question. The title seems implicitly important. The initial challenge will be to define and measure "health impact" and "chronic recurrent rhinosinusitis."

2. Medical logic and ethics: purpose of the researchable question. Let us say that we can find a validated test that measures "health impact for children," Procedure A, and that we can define, by an aggregate of signs, symptoms, and tests that identify what we mean by "chronic recurrent rhinosinusitis," Disease X. On face value, it would appear to be ethical to measure the "health impact" in this disease as we treat it in practice.

The Disease X will be treated in our practice by a variety of maneuvers depending on the severity of the disease and the response to initial and progressive treatments. Hence, we might expect Disease X to be a hetero-

geneous spectrum of disease, perhaps measurable in severity by an ordinal scale, such as the following: (best) 0–1–2–3–4–5 (worst). Or, we might choose to make it a binary nominal variable as follows: Disease X, present or absent, regardless of severity.

Procedure A might also have an ordinal scale with a limited number of values, or it may have a wide range of values, ranging from 0 to 100.

We now have some idea of structure, but what might our question be? Rather than guess, let's take a look at the report briefly. The objective is to ". . . quantify the health-related quality of life of children *who require surgical intervention. . .*" That answers one question; the Disease X is likely to be a nominal variable, present or absent. In fact, the way the objective is stated, Disease X may not vary in the proposed study; therefore, it will not be a variable.

Let's say that child 1 has a Procedure A value of 80 and child 2 has a value of 34, and so forth; we will have a long (or short) array of quasidimensional values describing the quality of life, with a mean and SD. So what will that mean? Don't we have to have something to compare it with, for it to have meaning?

It seems logical to compare our group of children with disease so severe that they require surgery with one or more control groups, measured by the same instrument. If we compare our group with normal children (a negative control), we will have the comparison in that direction, but we still will not have a clear idea of just how bad this is. If we then compare our group with known severe diseases in children (a positive control), we will have our group bracketed and have a better understanding of the quality of life for this group. Included in the positive and negative control groups, it would seem logical to compare our group of children with those that do not require surgery.

3. Identification of variables. If our logic holds, the independent, or predictor, variable should be “Disease” with the following levels: our group of surgically treated children with chronic rhinosinusitis, normal children, children with medically treated chronic rhinosinusitis, and several groups of children with other diseases in which the same instrument, Procedure A, is applied. The dependent, or outcome, variable will be the results of Procedure A.

4. Data display and research logic. This is a survey study, not an experiment; randomization is not germane. This is a cross-sectional study in which all data will be obtained at once; the baseline condition (i.e., the disease), the Procedure A, and the procedure results, outcome, will all be available at the same time. Several groups, assembled by the baseline normal state or disease, will be assessed and compared.

The data is likely to be arrays of quasidimensional strings and to be contrasted by indexes appropriate for dimensional data; again, refer to Table I in the first of this series of reports¹ to view the statistical tools that may be appropriate.

5. Original data source. If we are correct in the assumption that a validated tool exists to assess quality of life in sick and normal children, large databases may exist containing protocol-obtained original data sets of normal and sick children. These databases might serve as historical controls, negative and positive, against which the prospective, protocol-acquired data from our group can be compared.

Another way to structure the study would be to prospectively perform Procedure A, the validated test of quality of life, on our own groups of normal and variously sick children as well as our surgical rhinosinusitis group.

6. Best selection from menu of prototypical approaches for assembly of subjects. See Table V.

The choice “Cross-Sectional Study—Assemble Subjects or Previous Original Data by Variable of Choice After Maneuvers and Outcomes Have Occurred” (Table V) would best fit the intent of the approach just analyzed. However, several groups would be conducted and compared. The data from one group would only be descriptive; conducting several groups, comparative research can be performed.

The actual study reported was a prospective survey design for the surgical rhinosinusitis group but did use historical data for comparisons.

Example 3

“Factors related to outcome of salvage therapy for isolated cervical recurrence of squamous cell carcinoma in the previously treated neck: a multi-institutional study.”¹²

The study just named is a good example of a multi-institutional study looking retrospectively at previously obtained original data sets that were generally protocol acquired because they were tumor registries. The information was assembled by disease, as the baseline state, and the research look was forward to outcome (surrogate for a longitudinal cohort); however, because this was pre-

viously obtained data, the approach is classified as a retrospective cohort study.

Example 4

“In my practice, I have medical records on patients with a disease of interest to me. I am interested in management. What study can I do with them?”

Let us consider that we are interested in attempting to determine the best treatment for Disease X. Because of being collected without a protocol, medical records are biased, filled with ambiguities, and flawed by missing data; the literature is full of reports on this type of material in the form of single case reports or case series. However, a leap from clinical case material to the idea of a randomized clinical trial may be too much of a task at first.

There are different ways to look at this available material that may help bridge the gap toward a randomized trial and yield useful information.

Case-Control Study

First, let's see if there are good results and poor results. Because the outcomes following treatment, just like the outcomes of exposures resulting in disease, can be used as cases and controls, we can assemble the poor results as “cases” and the good results as “controls.”³ We can then conduct a case-control study looking at the demographics, comorbidities, and other predisease state demographic attributes from the medical history, as well as the various interventions used to try to determine whether any of these antecedent attributes and/or therapies seem to significantly differ between the poor-result “cases” and the good-result “controls.”

Retrospective Cohort Study

We might take a different group of medical records (from a colleague, or ours) and use the hypothesis generated by the case-control study. This time, we assemble the subjects according to the demographic variable or maneuver that appeared to make a difference and seek to ascertain the outcome in these different groups. If this also supports that the maneuver or demographic variable seems to make a difference in outcome, we may be ready to conduct a prospective study.

Prospective Cohort Study

From what we have now read and discovered from our own data, we know exactly what questions to ask the patient in the history and physical every time, and what standard interventions we wish to test to see whether there really is a difference.

Maybe the difference is the intervention, or maybe the difference is attributable to prognostic factors on which we have intuitively based our treatment decisions. We can determine this.

If we use this information to create protocol data entry forms (i.e., a history, physical examination, and a repetitively structured follow-up form that asks the pertinent questions and requires a positive or negative answer every time), we now have the beginning of a prospective cohort study of this group of patients. If we formulate a

hypothesis from our previous data, we will soon be able to have enough data to test the hypothesis.

Randomized Clinical Trial

If the prospective cohort study indicates that one treatment is really better than another, we can use that information as a generated hypothesis to support a randomized clinical trial, which we are well prepared to conduct, now, in our own clinical practice.

CONCLUSION

Clinical experience is not only what one does but also what one reads and assimilates; if poor information is assimilated into one's experience, it begins to degrade the experience.

The purpose of this report was to assist the busy practitioner to define a clinical question in a researchable way and to rapidly determine the types of clinical research studies that are likely to yield valid information about a specific question.

The tables serve as a rapid reference section. The initial two-part narrative explains the process of approach selection. The examples section illustrates the application of the selection algorithm.

Our contention is that, the more we know about clinical research, the more efficient we become in the rapid retrieval and assessment of pertinent and valid evidence. The more we know, the more we construct a POWERFUL 10-MINUTE OFFICE VISIT.

The next Tutorial will address biases and how they may be minimized.

BIBLIOGRAPHY

1. Neely JG, Hartman JM, Wallace MS. Building the powerful 10-minute office visit, I: introduction to the new section. *Laryngoscope* 2000;110:1595-1601.
2. Neely JG, Hartman JM, Wallace MS. Tutorials in clinical research: building the powerful 10-minute office visit, II: beginning a critical literature review. *Laryngoscope* 2001; 111:70-76.
3. Feinstein AR. *Clinical Epidemiology: The Architecture of Clinical Research*. Philadelphia: WB Saunders, 1985.
4. Hearst N, Hulley SB. Using secondary data. In: Hulley SB, Cummings SR, eds. *Designing Clinical Research: An Epidemiologic Approach*. Baltimore: Williams & Wilkins, 1988:53-62.
5. Portney LG, Watkins MP. *Foundations of Clinical Research: Applications to Practice*. Norwalk, CT: Appleton & Lange, 1993.
6. Hulley SB, Cummings SR. *Designing Clinical Research: An Epidemiologic Approach*. Baltimore: Williams & Wilkins, 1988.
7. Fletcher RH, Fletcher SW, Wagner EH. *Clinical Epidemiology: The Essentials*. edn 2. Baltimore: Williams & Wilkins, 1988.
8. Sackett DL, Haynes RB, Tugwell P. *Clinical Epidemiology: A Basic Science for Clinical Medicine*. Boston: Little, Brown, and Company, 1985.
9. Sackett DL, Richardson WS, Rosenberg W, Haynes RB. *Evidence-Based Medicine: How to Practice and Teach EBM*. New York: Churchill Livingstone, 1997.
10. Massick DD, Welling DB, Dodson EE, et al. Tumor growth and audiometric change in vestibular schwannomas managed conservatively. *Laryngoscope* 2000;110:1843-1849.
11. Cunningham MJ, Chiu EJ, Landgraf JM, Gliklich RE. The health impact of chronic recurrent rhinosinusitis in children. *Arch Otolaryngol Head Neck Surg* 2000;126: 1363-1368.
12. Krol BJ, Righi PD, Paydarfar JA, et al. Factors related to outcome of salvage therapy for isolated cervical recurrence of squamous cell carcinoma in the previously treated neck: a multi-institutional study. *Otolaryngol Head Neck Surg* 2000;123:368-376.