Published in final edited form as:

Am J Med. 2014 May ; 127(5): 379–384. doi:10.1016/j.amjmed.2014.01.011.

Individual and Composite Study Endpoints: Separating the Wheat from the Chaff

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Abstract

We provide an overview of the individual and combined clinical endpoints and patient reported outcomes typically used in clinical trials and prospective epidemiological investigations. We discuss the strengths and limitations associated with the utilization of aggregated study endpoints and surrogate measures of important clinical endpoints and patient-centered outcomes. We hope that the points raised in this overview will lead to the collection of clinically rich, relevant, measurable, and cost-efficient study outcomes.

Keywords

Clinical epidemiology; study design; study outcomes and endpoints

Introduction

The information obtained and reported from observational clinical/epidemiological research studies and randomized clinical trials (RCTs) provides clinicians, health policy makers, and prevention oriented practitioners with much needed information about the causes of disease, their prevention, and the most effective ways to manage and improve the prognosis of persons diagnosed with disease as well as improve the general health status of communities^{1–4}. The validity, reliability, and relevance of these studies is based, in part, on the size and descriptive characteristics of the study population, their representativeness to

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Conflict of Interest Statement: There are no conflicts of interest for any of the authors. All authors had access to the data and a role in writing this manuscript.

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the broader universe of patients with the condition under study, accurate measurement of key exposure and potentially confounding factors, and careful and unbiased assessment of primary and secondary study endpoints.

While observational epidemiologic investigations and RCT's remain the cornerstone approaches in the development and evaluation of new therapies and lifestyle intervention approaches, especially the "gold standard" RCTs, these investigations are often scientifically and logistically complex with considerable costs associated with their design, conduct, and analysis. Given the enormous costs, resources, and logistics involved in carrying out these investigations, researchers and funding agencies continue to explore novel approaches and strategies, such as pragmatic clinical trials and quasi-experimental designs, that would result in more efficient and cost effective approaches to the enhanced primary and secondary prevention of chronic and infectious diseases at both the individual and community level⁵⁻⁹.

The selection of carefully considered, measured, and categorized study outcomes in these investigations is crucial to the successful assessment, meaning, and eventual incorporation of the study results into clinical practice and broader public policy initiatives. Randomized trials and appropriately designed and performed observational studies can provide complementary insights into a broad range of clinical problems, particularly in the current era of more widespread implementation of electronic health records at individual medical practices and in larger health care systems¹⁰. To provide meaningful results, these investigations must have sufficient statistical power to address clinically important questions, balance a variety of known and unknown potentially confounding factors between the respective comparison groups (in RCT's), and provide estimates of treatment effects with narrow confidence intervals.

The purpose of this article is to describe the use of individual and combined clinical endpoints and patient reported outcomes in clinical research studies and the strengths and limitations associated with the utilization of aggregated endpoints and surrogate measures of important clinical outcomes.

Study Endpoints

There are a variety of endpoint/outcome measures that can be investigated in a clinical/epidemiological research project. These include patient associated morbidity (e.g., recurrent episodes of disease), mortality (total and cause-specific), quality of life (general and disease-specific), health services utilization, and changes in various lifestyle practices and physiologic parameters over the course of an observational longitudinal study or RCT.

In addition to the conventional "hard" (e.g., morbidity, mortality) event type endpoints typically examined in clinical research investigations, and more "soft" study endpoints such as hospitalizations, symptomatology, and changes in selected physiologic measures, patient-reported outcomes are increasingly being used in the study of chronic diseases and their precursor conditions. These outcomes represent the status of a patient's health condition that are elicited directly from the patient without any interpretation of the patient's responses by a health care provider¹¹. These outcomes are being utilized on a more frequent basis in clinical research since they are of considerable importance to patients and their families, are

able to be effectively measured with standardized instruments, are generally brief in nature, and can utilize different means of administration to assess these self-reported outcomes over the course of a longitudinal study or RCT^{12–15}. For example, questionnaires assessing quality of life, social support, and cognitive status are increasingly being used in research studies as are more novel approaches such as cell phone applications to record daily pain levels in patients with various underlying illnesses, such as rheumatoid arthritis. Indeed, the CONSORT (CONsolidated Standards Of Reporting Trials) statement has been recently updated to include standards for reporting patient centered outcomes in RCT's^{12,15}.

Use of Single Versus Multiple Study Clinical Endpoints and Patient Reported Outcomes

The majority of observational studies and RCT's pre-specify both a primary and, typically, several secondary study endpoint/outcomes, and estimate the sample size for the study based on clinically meaningful differences in the primary study outcome between intervened and non-intervened individuals in RCT's and between exposed and non-exposed individuals in longitudinal studies. For example, many clinical trials that have evaluated the use of novel therapies in patients hospitalized with acute myocardial infarction have examined differences in hospital case-fatality rates between patients receiving, as compared to those not receiving, a study drug of interest and have estimated the sample size for these trials based on what were considered to be meaningful differences in the primary trial outcome of all-cause mortality.

Clinical and public health researchers need to carefully consider the pertinent endpoints they intend to monitor *a priori*, and the accuracy, time, and costs associated with their measurement and potentially independent validation/adjudication. Indeed, even the choice of more conventional "clinical" outcomes can be fraught with difficulty in measurement and interpretation.

For example, the multi-center REACT (Rapid Early Action for Coronary Treatment) trial was designed to examine the effects of a multi-pronged community intervention on patient's care-seeking behavior in adults presenting with signs and symptoms of acute coronary disease to more than 40 hospitals in 10 states throughout the U.S.¹⁷. This trial recruited enough patients to detect meaningful differences in pre-hospital delay times in the 10 pair-matched intervention and reference communities¹⁷. This principal trial outcome was defined as the time interval from self-reported acute symptom onset to arrival at the emergency department, as recorded in hospital medical records. However, the quantification of patient's care-seeking behavior is fraught with potential difficulties and problems, including the extent and accuracy of patient recall and the systematic elicitation and recording of this information by health care professionals. Furthermore, in observational studies and clinical trials, to standardize classification of what may appear to be a relatively straightforward "hard" clinical endpoint, such as cardiovascular related mortality, a study adjudication committee may be created to develop pre-defined criteria for this endpoint.

Effect of endpoint selection on study sample size

Once the primary study outcome has been agreed upon, the investigators will need to determine, especially for longitudinal studies that involve following patients over a prolonged period of time, their sample size needs under a variety of working assumptions of: study drug treatment effects, possible study drop-outs and losses to follow up, medication adherence, length of study duration, and magnitude of relative and absolute differences between respective comparison groups. Most clinical trials and observational studies also include several secondary study outcomes, each typically linked to the mechanisms of action or adverse effects of the RCT intervention, or the effects of the exposure variable on various organ systems and physiologic parameters in a prospective cohort study.

If the primary endpoint of an RCT is either the development of a serious clinical complication or death, depending on the characteristics of the study population and the study design, this endpoint may occur infrequently, implying an increase in the number of patients needed to detect a clinically meaningful effect of the intervention being assessed.

Since obtaining an adequate number of clinical endpoints in an RCT or cohort study often requires large numbers of subjects to be followed for a prolonged period of time, clinical researchers may restrict their study population to persons at greatest risk for the principal study outcome. This restriction, which is expressed through the study's pre-delineated inclusion/exclusion criteria, however, may limit study generalizability as the results of the investigation may only apply to individuals with characteristics similar to those enrolled in a specific trial or observational study.

Composite Endpoints

Because of the need to observe a certain number of primary endpoints to achieve adequate statistical power for a study, investigators may opt to use a composite, or aggregated, study endpoint, in which the occurrence of any one of a set of multiple outcomes is classified as an outcome. A related concept is the use of a surrogate marker or endpoint, which is the use of an indirect measure(s) of actual and more conventional clinical endpoints to avoid repeated invasive procedures (e.g., liver biopsies) or for other study related reasons.

In a number of RCTs, especially those in the heavily researched area of cardiovascular disease, investigators will often combine several outcomes into a single composite study endpoint^{18–22}. For example, researchers have examined the effects of different cardioprotective medications and interventional approaches on the development of nonfatal and fatal myocardial infarctions, strokes, and all-cause or cause-specific mortality. These combinations of endpoints have often been referred to as MACE (major adverse cardiac events)^{18,21}; an endpoint is classified as having taken place with the first occurrence of any one of these pre-delineated events. Composite endpoints have also been used in the design and conduct of RCT's in other medical specialty areas (e.g., anesthesia, emergency medicine) and disease states (e.g., pulmonary disease, gastrointestinal disorders)^{14,23–25}.

Combining two or more study outcomes into a single composite measure typically results in an increase in the incidence rates of the composite endpoint under investigation and

improves the ability to detect clinically meaningful differences in the primary study endpoint due to the increased statistical power from the higher number of endpoints. This pooling of different study outcomes will result in higher event rates and increased statistical precision that will subsequently lead to designing clinical trials that include fewer patients, are less costly, and can be completed in a more timely manner.

On the other hand, in aggregating individual study endpoints into a composite outcome measure, there is an inherent assumption that each component of this pooled endpoint will have a similar impact on health, will change in the same “direction” with regards to the active treatment, and will be of equal importance to patients and their providers; this assumption is often not satisfied, however. For example, patients and/or their immediate family members may be extremely concerned about the development of a disabling stroke and being functionally incapacitated and unable to perform their activities of daily living while being less concerned with the development of intermittent episodes of dyspnea.

Indeed, an expert panel has recently recommended monitoring several health measures that are important for older persons with multiple chronic conditions in lieu of more conventional “hard” morbidity or mortality endpoints²⁶. This NIA-AHRQ convened panel recommended that older adults with multiple chronic physical and mental health conditions be assessed with regards to their general health status, pain, fatigue, gait speed, and on their physical health, mental health, and social role function through the use of standardized measures²⁶. Insights into these endpoints would provide meaningful and useful information for patients, their families, and their health care providers which would hopefully lead to improved relevant health outcomes in these individuals.

The aggregation of individual study outcomes into a single composite measure has, however, led to consideration of the weighting of trial endpoints, as well as need to balance the efficacy and safety components of each endpoint included in a composite outcome measure²⁷. This concern is based on the assumption that a similar direction of the effect of the intervention will occur for each component of an aggregated outcome. Ideally, readers of published articles can see the actual incidence rate of each individual component of a composite endpoint so that they can decide for themselves how to interpret the results of the study and how to best counsel their patient populations.

For example, in the Physician’s Health Study, differences in a number of individual clinical endpoints were examined between patients treated with low-dose aspirin and beta carotene in a two-by-two factorial design²⁸, including nonfatal and fatal myocardial infarction, nonfatal and fatal stroke, death due to a cardiovascular cause, death due to a non-cardiovascular related condition, and all-cause mortality²⁸. If multiple events occurred in the same patient, a coding system was developed to determine how to count and classify the occurrence of a first cardiovascular event.

While the results of this large and carefully conducted clinical trial demonstrated favorable effects of the aspirin intervention on several individual study endpoints, including fatal and nonfatal myocardial infarctions, there was a non-significant increase in the risk of stroke, with an increased risk of hemorrhagic strokes in association with the prescribing of aspirin.

While a less than expected number of events occurred in the trial population which placed further caveats on the interpretation of the overall favorable trial findings, investigators need to be particularly thoughtful about the pooling of individual study endpoints into a single composite measure in designing a trial. Different effects of the trial intervention might be observed on the individual trial endpoints which would be subsequently blurred when aggregated into a single composite outcome. For example, if events of acute myocardial infarction and episodes of major bleeding were combined into a single composite trial endpoint, the overall net beneficial effect of a trial medication might be non-significant if the incidence rate of myocardial infarctions was decreased, but there was a concomitant increase in the risk of major bleeding episodes. The individual data showing these counterbalancing effects should be reported in the study publication so that physicians and their patients can make informed decisions about the use of the drug, weighing the specific pros and cons of utilization against the development of any detrimental clinical endpoints.

Surrogate Endpoints

Surrogate markers, often biological in nature, are increasingly being used to provide an indirect measure of the actual clinical endpoints that would ideally be studied in a longitudinal study or RCT if time and resources permitted. The use of “appropriate” and “clinically meaningful” surrogate endpoints may result in shortening the duration of the trial, reducing the number of subjects needed, and minimizing the costs and resources required to complete an RCT and/or prospective investigation.

A surrogate endpoint can take many forms, which will influence study related costs, logistics, and measurement. A surrogate endpoint can be in the form of a serum, salivary, or urinary chemical or physiologic biomarker, as a more subjective patient reported outcome, such as changes in symptom severity or patient’s functional status, or as changes in the extent of underlying disease through the use of noninvasive detection measures (e.g., b-mode carotid ultrasonography). In particular, serum biomarkers, such as changes in the serum levels of C-reactive protein or total cholesterol, and physiologic measures, including changes in the levels of blood pressure and forced vital capacity, are frequently utilized as surrogate trial endpoints. The choice of the surrogate endpoint should be approached with caution, since these measures may be crude or relatively reflective surrogates for the trial primary endpoint and may result in an increased sample size^{29–31}. Indeed, even a validated biomarker may have substantial variability in both its physiologic expression and its association with the clinical outcomes of interest, which may adversely affect the study sample size and study duration.

For example, the Food and Drug Administration recently announced the fast-track approval of a new drug to treat multi-drug resistant tuberculosis based on the findings from a surrogate measure (i.e., sputum culture results), rather than on the results from the measurement of a specific clinical outcome (i.e., chest x-ray), based on data from two small published studies³². In an editorial that discussed the approval of this drug, the pros and cons of surrogate measures were highlighted and the importance of carefully considered surrogate measures and relevant clinical endpoints, such as disease progression and death, was emphasized³². A recent editorial discussed the perils of relying on surrogate outcome

measures and the potential for patient harm through the use of these proxy measures on patient associated morbidity and mortality³¹.

Illustrative examples of individual trial endpoints, composite outcomes, and surrogate study measures in observational studies and RCT's in the areas of cardiovascular disease, pulmonary disease, and gastrointestinal disease are shown in Table 1.

Summary and Conclusions

There have been considerable advances in the design, conduct, and analysis of observational studies and individual and community-based RCT's, as well as in the measurement of key predictor and outcome variables. Furthermore, given the complexity, duration, and costs associated with these longitudinal studies, as well as the inclusion of patient-reported measures of personal and clinical importance, researchers and policy makers are devoting considerable time and resources to the discussion of clinically relevant, measurable, and cost-efficient study outcomes. Review groups for funding organizations are also paying close attention to the proposed endpoints for a study to ascertain their relevance to the disease, impact on study related logistics, and on the reporting of results.

There is an increasing focus on the use of composite and surrogate endpoints in clinical research and these endpoints are increasingly being utilized in RCTs. The use of these endpoints, however, needs to be carefully considered in the broader context of clinical efficacy and safety of the intervention being evaluated^{34,35}.

Researchers have an important role to play in this exchange of information by designing and conducting clinically meaningful observational studies and RCT's, finding cost efficient and reliable means to measure pertinent study predisposing and outcome variables, and completing these trials in a timely manner to distill and distribute information from these investigations to the improvement of an individual's and population's health status.

Acknowledgments

Funding support for this article was provided by the National Institutes of Health (RO1 HL35434). Partial salary support for Drs. Goldberg and Gore was provided for by the National Institutes of Health grant 1U01HL105268. The development of this publication was partially supported by the National Center for Advancing Translational Sciences of the National Institutes of Health under award number UL1TR000161 (Dr. Barton).

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Clinical Significance

- Issues involved in the collection and measurement of high quality and meaningful outcomes data in clinical and epidemiological research investigations are discussed.
- Collection of clinical endpoints and patient reported outcomes, use of single versus multiple study endpoints, pre-specification of primary and secondary study outcomes, effect of endpoint selection on study sample size, and strengths and limitations of using composite and surrogate endpoints are highlighted.

Table 1

Cardiovascular Disease		
Individual Endpoint	Composite Endpoint	Surrogate Endpoint
Total and cause-specific mortality	CVD mortality/MI/stroke	Serum levels of C-reactive protein
Disease recurrence (e.g., MI, angina, stroke)	Fatal or nonfatal MI/stroke/heart failure	Serum cholesterol levels
Bleeding	Hospitalization for MI/stroke	Blood pressure findings
Vascular complications		Frequency and type of cardiac arrhythmias
Quality of life		Anginal symptoms
Functional status		6 minute walk test
Pulmonary Disease		
Individual Endpoint	Composite Endpoint	Surrogate Endpoint
Total and cause-specific mortality	Progression-free disease survival (death or decline in forced vital capacity)	Serum IgE levels
Respiratory symptoms (e.g., cough, wheezing)	Exercise capacity	Multiallergen screen
Disease exacerbations		Nitric oxide
Quality of life (e.g., asthma quality of life questionnaire)		Complete blood count
Gastrointestinal Disease		
Individual Endpoint	Composite Endpoint	Surrogate Endpoint
Total and cause-specific mortality	Sustained disease remission without treatment (e.g., corticosteroids) and mucosal healing	
Clinical remission	Bowel damage scores	
Hospitalization		
Mucosal healing		