



The Clinical Aspects of Claim Substantiation: The Concept of Cause-and-Effect

by Ioana Carabin, M.D.

This article—the last of a series¹ to acquaint the reader with the theory and lexicon of clinical testing—focuses on the concept of cause-and-effect in medicine and clinical trials, although it is not intended as a comprehensive overview of the vast and complex topic of causal criteria.

Cause-and-effect is not exclusive to the field of medicine, and dates as far back as Aristotle.² Philosophers generally define causality as the relationship of a cause to an effect, and accept the concept that given circumstances under controlled conditions must inevitably produce standard results. For example, Immanuel Kant³ said that “cause” is a fundamental category of understanding and a necessary condition for experience.

Care of the sick has been practiced for millennia, at times under cause-and-effect assumptions. Such thinking was evident in the Middle Ages, when banning people with communicable diseases from cities and placing disease-ridden ships under quarantine were common practices. It was not until the 19th century that Friedrich Henle⁴ and Robert Koch⁵ would revolutionize the scientific world by formulating postulates from which the inference could be made that a specific living organism caused a particular disease. In simplified form, these postulates were:

- The organism is always found with the disease.
- The organism is not found with any other disease.

- The organism, cultured from one with the disease and cultured through several generations, produces the disease.

In 1876, theory became reality when Koch demonstrated that anthrax met these three criteria. The concept was radical—it correlated a specific agent to a disease for the first time—and it opened the door for new interventions such as vaccines.

One hundred years later, the *U.S. Surgeon General's Report*⁶ implicated smoking as a cause of lung cancer and generated much controversy as to whether such causal thinking could be applied to other chronic diseases. Soon thereafter, Sir Austin Bradford Hill⁷ published an article⁸—one of the most cited papers in health research—outlining a systematic approach in epidemiology that could be used to judge when an association might be causal. Hill never used the term “criteria” and he stated that all nine “viewpoints” were neither necessary nor sufficient for demonstrating causation. The viewpoints are summarized below, following Hill's original ranking.

Hill's Causation Viewpoints

- (1) *Strength.* A strong association is more likely to be causal than a weak one. Hill warned against making a quick decision against a weak association, however, as it does not always rule out causality.
- (2) *Consistency.* If the association is observed repeatedly in different populations in different settings, it is more likely to be causal than an isolated observation.
- (3) *Specificity.* A cause should lead to a single and not multiple effects.
- (4) *Temporality.* A cause must precede an effect in time.



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- (5) *Biological gradient*. This is the presence of a dose-response gradient; if more of a dose leads to more of an effect, this supports the idea of causality.
- (6) *Plausibility*. The idea of causation must be biologically plausible.
- (7) *Coherence*. The idea of causation must accord with other observations. The absence of coherent information, however, does not rule out a causal relationship.
- (8) *Experimental evidence*. Supporting data from human or animals experiments helps establish a causal relationship.
- (9) *Analogy*. In certain circumstances, assessment of a causal association could be done by analogy; this may be helpful, but is not required to make a determination.

In addition to these “criteria,” Hill made several other points including that statistical significance should not be mistaken for evidence of a substantial association, and an association does not prove causation—other evidence must be considered.

Causal Association in Medicine

Hill’s article established that using criteria to determine a causal association in medicine is paramount. In modern days, the concept of causal inference impacts most aspects of medicine; from the individual patient being treated for a specific acute or chronic condition, to global immunizations to eradicate deadly contagious diseases, to clinical trials in the quest of finding new cures.

In medicine, what often is meant by causation actually is an increased probability. For example, we are accustomed to hearing that cigarette smoking *causes* lung cancer, when a more accurate statement is that smoking increases the *probability* that an individual will develop lung cancer; many people who smoke do not develop lung cancer, and some individuals that never smoked do develop lung cancer. This probability ranks fairly high. On the other hand, the probability is very low that drinking a glass of wine per day will *cause* liver failure.

Another term sometimes used interchangeably with cause is “risk factor”—“a single characteristic statistically associated with, although not necessarily causally related to, an increased risk of morbidity or mortality (e.g., smoking as a risk factor for heart disease).”⁹ For example, it is universally accepted that diabetes, hypertension, and obesity¹⁰ are several risk factors for developing cardiovascular disease.

Even more difficult is deciding on causation for an individual case, as seen when patients ask their physicians

if exposure to an individual agent in their workplace might have caused a certain condition (e.g., a person working in a bakery wondering if daily exposure to flour has led to the development of rhinitis). Importantly, the patient also wants to know how certain the physician is about such causation.

Despite public belief and hope, medicine is not an exact science. Physicians act with a measure of uncertainty, especially in emergency situations where time is of the essence. For example, surgeons will assess the signs and symptoms, make a diagnosis, and recommend surgery—a process based on probability and not 100% certainty, and predicated on clinical experience and standard of care. Waiting to reach 100% certainty can jeopardize a patient’s life (e.g., delaying an appendectomy for a likely diagnosis of appendicitis or a tracheostomy for increased airway swelling). This process has been acknowledged in the United States and coined as “reasonable medical certainty”; it has been defined by the courts¹¹ to mean “more certain than not,” which amounts to only 51% certainty.

Causal Association in Vaccinations

The concept of cause-and-effect has applicability in all medical disciplines, probably best exemplified by global immunization efforts/programs. Since the inception of vaccination, it has been recognized that adverse events following immunization (AEFIs) will occur at a frequency directly related to the number of vaccine doses administered. AEFIs can be causally related to the inherent properties of the vaccine, or linked to errors in the administration, quality, storage, and transport of the vaccine. Vaccination programs throughout the world have acknowledged that when large populations are vaccinated, some serious events that occur rarely—with or without vaccination—will be observed coincidentally following vaccination.

Assessing the causality of AEFIs is challenging, and eventually became the focus of the Immunization Safety Priority Project launched by the World Health Organization (WHO) in September 1999. The ability to respond promptly and effectively to vaccine safety concerns was the center of the project, leading to the development of the Global Advisory Committee on Vaccine Safety (GACVS). The Committee set out to develop criteria for judging encountered adverse effects post vaccination and categorizing them. WHO defined a “probable causal association” as one where there is a reasonable time sequence, the event is unlikely to be attributable to concurrent disease or other medicines, and a clinically reasonable response follows withdrawal. On the

other hand, a “possible causal association” was designated as requiring a reasonable time sequence, but the event also may be explained by concurrent disease or other medicines, and information on withdrawal may be lacking or unclear. The criteria employed by WHO to assess the causality of association vis-à-vis vaccinations utilizes several principles initially outlined by Hill. WHO indicates that not all of the criteria need to be present, nor does each carry equal weight for determining a causal relationship between an adverse event and a vaccine. WHO’s criteria include:

- (1) *Consistency*. The association of an alleged adverse event with the administration of a vaccine should be consistent (i.e., the findings should be replicable in different localities, by different investigators, and using different methods of investigation).
- (2) *Strength of association*. The association should be strong in the magnitude of the association (in an epidemiological sense), and in the dose-response relationship of the vaccine with the adverse effect.
- (3) *Specificity*. The association should be distinctive and the adverse event should be linked uniquely or specifically with the vaccine concerned, rather than its occurring frequently, spontaneously, or commonly in association with other conditions.
- (4) *Temporal relation*. Receipt of the vaccine should precede the earliest manifestation of the event or a clear exacerbation of an ongoing condition (e.g., an anaphylactic reaction occurring seconds or minutes following immunization would be strongly suggestive of causality, as opposed to such reaction weeks later).
- (5) *Biological plausibility*. The association should be plausible and explicable biologically according to known facts in the natural history and biology of the disease. Biological plausibility is most helpful when it is positive; it is less so when negative.

Causal Association in Clinical Trials and Claim Substantiation

Human trials represent the testing grounds for assessing cause-and-effect under controlled situations. Therefore, several epidemiological principles described (i.e., Bradford-Hill criteria), are applicable regardless of the hypothesis being investigated. As explained in earlier articles in this series on claim substantiation,¹² a health claim can be made for a food or supplement ingredient provided the claim is substantiated by clinical trial data. By definition, a health claim has two essential components: a substance and a disease¹³ or health-

related condition. The basic objective in any clinical trial is that of demonstrating a cause-and-effect relationship—in this case to demonstrate that a known or novel dietary supplement ingredient (or a dietary supplement product) has an effect on a particular health-related condition.

Thoroughness, totality, and quality of the clinical data submitted while petitioning the Food and Drug Administration (FDA) is critical. Credibility of the clinical data is established on well-defined, reproducible, and unbiased response criteria.¹⁴ Further, well-conducted human studies have to demonstrate a clear association in a study design that is determined *a priori* for testing the hypothesis of such association. There are several clinical study designs commonly used; in decreasing order of probability for achieving the objective of the study, these are: randomized controlled clinical trials, cohort studies, case-control studies, and controlled case-series analyses. Case reports, regardless of their numbers, do not fulfill the requirements for testing hypotheses. According to FDA, randomized clinical trials remain the “gold standard” in clinical study design, specifically prospective, blinded or double-blinded, controlled studies.

The randomized controlled study is highest-ranked by the agency in the Qualified Health Claim (QHC)¹⁵ submission process, provided such a study is adequately developed and conducted. This approach has been criticized by the American Evaluation Association (AEA),¹⁶ however, which argues that randomized control group trials (RCTs) have their weaknesses (e.g., ethical issues) and are not the only studies capable of generating understandings of causality. According to AEA, in medicine, causality has been conclusively shown in some instances without RCTs (e.g., smoking and lung cancer, and infested rats and the bubonic plague).

Both FDA and the Federal Trade Commission (FTC)¹⁷ require demonstration of statistical significance in clinical trial data submitted for claim substantiation. The information obtained from the rigid, clearly unrealistic settings¹⁸ required by clinical trial protocols—compared to real-life situations—is important for new medical treatments, development of medical guidelines, and health policies. It remains unclear, however, how well this information correlates—or whether a correlation even should be sought—to the “reasonable medical certainty” principle applied in clinical practice.

In clinical trials, it is not possible to demonstrate a cause-and-effect relationship with 100% certainty, but it is possible to establish a degree of probability. Nonetheless, adhering to sound investigative principles while designing and conduct-

ing a clinical trial will always enhance the credibility of the data, thus bringing one closer to substantiating a claim. Δ

¹ For an overview of claim substantiation, see Ioana G. Carabin, *The Clinical Aspects of Claim Substantiation*, FDLI UPDATE, May/June 2004, at 25; Ioana G. Carabin, *The Clinical Aspects of Claim Substantiation: Clinical Trial Costs*, FDLI UPDATE, July/Aug., 2004, at 39.

² Aristotle (384-322 B.C.).

³ Immanuel Kant (1724-1804).

⁴ Friedrich Gustav Jakob Henle (1809-1885).

⁵ Robert Koch (1843-1910).

⁶ U.S. DEP'T OF HEALTH, EDUCATION & WELFARE, SMOKING AND HEALTH: REPORT OF THE ADVISORY COMMITTEE TO THE SURGEON GENERAL OF THE PUBLIC HEALTH SERVICE (PHS Pub. No. 1103) (1964).

⁷ Austin Bradford Hill (1897-1991); an English epidemiologist and statistician who pioneered rigorous statistical study of patterns of disease.

⁸ Austin Bradford Hill, *The Environment and Disease: Association or Causation?*, 58 PROCEEDINGS OF THE ROYAL SOCIETY OF MEDICINE 295-300 (1965).

⁹ STEDMAN'S MEDICAL DICTIONARY (1996).

¹⁰ For general information on this topic, see Ioana G. Carabin & George A. Burdock, *Obesity in the United States: An Overview*, FDLI UPDATE, Jan./Feb. 2005, at 9.

¹¹ Glenn E. Bradford, *Dissecting Missouri's Requirement of "Reasonable Medical Certainty,"* 57 J. Mo. BAR 136 (May 2001).

¹² See *supra* note 1.

¹³ "Disease" is defined in 21 C.F.R. § 101.14(a)(5) as "damage to an organ, structure or system of the body such that it does not function properly (e.g., CHD), or a state of health leading to dysfunctioning (e.g., hypertension)."

¹⁴ *Id.*

¹⁵ Qualified health claims are made when there is emerging evidence for a relationship between a food, food component, or dietary supplement and reduced risk of a disease or health-related condition. In this case, the evidence is not well enough established to meet the significant scientific agreement standard required for FDA to issue an authorizing regulation. Qualifying language is included as part of the claim to indicate that the evidence supporting the claim is limited. See FDA/CFSSAN/ONPLDS, CLAIMS THAT CAN BE MADE FOR CONVENTIONAL FOODS AND DIETARY SUPPLEMENTS (issued Mar. 20, 2001; rev. Oct. 2001 & Sept. 2003).

¹⁶ Notice of Proposed Priority: Scientifically Based Evaluation Methods, 68 Fed. Reg. 62,445-47 (Nov. 4, 2003) (RIN 1890-ZA00, Amer. Evaluation Ass'n Response to U.S. Dep't of Education).

¹⁷ The FTC's primary responsibility for claims is to ensure that claims made in advertising are truthful, not misleading, and substantiated.

¹⁸ Demographic variables, age, and any comorbidities will determine if the trial population closely resembles the patient population. Thus, they also will determine the generalizability of the study findings.



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