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THE POWER OF META-ANALYSIS: HOW SMART COMPANIES ARE USING A STATISTICAL METHODOLOGY TO DRIVE BREAKTHROUGHS

Written By

Denise Ryan, M.L.I.S., Nerac Medical Device Analyst

Perry De Fazio, Nerac Medical Device Analyst

Deborah Schenberger, Ph.D., Nerac Medical Device Analyst

In This Publication

INTRODUCTION

No longer do the most impressive, headline-grabbing breakthroughs come from clinical studies performed on massive numbers of patients and through years of study by a single, dedicated research team. Instead, the breakthroughs are coming from smart businesses and researchers who compile data from dozens of clinical studies from around the world, pooling the results into one, giant meta-analysis.

Often, businesses find that they cannot perform a clinical study with enough patients to provide statistical significance to the results, so they must combine their results with those of others to determine safety and efficacy. Other businesses feel their products are far superior to others currently on the market, but to gain market share, they need to demonstrate the benefits of their products across a large cross-section of the population. Whatever the reason, meta-analyses are powerful tools that the medical device industry can use to promote and gain approval for innovative new products.

Meta-analysis is a statistical technique that incorporates quantitative methods to combine the results of similar, but not necessarily identical, studies. Meta-analysis can also fall under the guise of a systematic review, a process that entails gathering all completed published studies from secondary literature specific to a targeted research question and subsequently applying meta-analysis techniques to answer that research question.

Researchers across various scientific, engineering, and business disciplines can apply a meta-analytical approach to better understand comparable research without having to have access to the raw data of each individual study. In the medical device or pharmaceutical world, meta-analyses are often used to investigate safety and efficacy, compare cost effectiveness of one treatment over another, help achieve regulatory approval, justify the expansion of indications for use, or as a requirement to justify further grant-funded studies.

THE VALUE PROPOSITION

Nerac surveyed authors from a random sample of meta-analyses published in Medline over the past year for insight into the motivation behind their research. Here is what they said about defining the value proposition of meta-analyses:

If performed correctly, a meta-analysis can help answer questions that may otherwise be difficult to answer for several reasons.

- Large studies or trials may not have been done on rare diseases, but there may be several small institutional studies that could be combined for analysis.
- Meta-analyses can help to reconcile conflicting results of smaller studies.
- Meta-analyses can be used to compare the efficacy of various devices on the market.
- Meta-analyses can evaluate and summarize the benefits and harms of particular types of treatments and help provide additional evidence related to safety and efficacy.
- Meta-analyses can be used to better evaluate treatment differences and rare side effects.

Several respondents emphasized that meta-analyses can be extremely effective if used *correctly*. In 1987, Sacks et al reviewed the quality of 86 meta-analyses conducted on randomized controlled trials across six criteria: study design, combinability, control of bias, statistical analysis, sensitivity analysis, and application of results. Only 28 percent of the analyses were

deemed to have addressed all six areas adequately.[1] As a result of these and similar findings from other methodological reviews, newer techniques and automated tools have evolved their functionality to address the issues related with earlier meta-analyses. While the tools used in conducting meta-analyses have improved, pitfalls are inherent to the method, primarily relating to the data that is used and the objectivity and skill of the reviewer. As one author simply stated, "Garbage in, garbage out."

Nerac has seen increasing numbers of clients that require product or technology validation. Or they are trying to find ways to separate their products from the competition. For these clients, Nerac conducts meta-analyses as a powerful way to accomplish those goals.

USE OF META-ANALYSES IS EXPANDING

Systematic reviews and meta-analyses are considered to be high-level evidence, and the number of these types of studies is increasing in the secondary literature. When looking at medical literature, the number of meta-analyses published has more than doubled in the last five years. Table 1 shows the increase in meta-analyses indexed as a document type in PubMed from 2003 to 2007.

Table 1. Meta-Analyses from PubMed 2003-2007

Year	2003	2004	2005	2006	2007
Meta-Analyses	1300	1629	2164	2524	2760

Not only has the use of meta-analysis grown within the clinical and scientific research arenas, it is also gaining in popularity and applicability in other circles, too. Organizations requiring applications for grant funding view meta-analyses and systematic reviews as acceptable types of research methodologies that can receive funding. An application form from the NHS, National Institute for Health Research in the United Kingdom, for example, has a specific section for types of research methodology listing the following:

- Clinical Trial , phase I, II, III, or IV
- Epidemiology
- Qualitative study
- Survey
- Cohort Study
- Meta analysis
- Retrospective review
- Systematic review

Guidelines from the National Institutes of Health grant program also referred to meta-analyses in the most recent version of its Program Organization and Coordination Conditions: "The use of common study variables, criteria, and protocols to facilitate meta-analysis of the studies when possible is highly encouraged." While these are but two examples, they each originate from large, national government funding bodies.

Papers from leading journals are also recognizing the usefulness of meta-analyses. In the May 2008 issue of KCONNECTION, a newsletter of the Kellogg Health Scholars program, the call for papers section mentioned that *Epidemiologic Reviews'* 2009 theme issue is focusing on health disparities. In the author instructions the call states: "Manuscripts can be up to 6,000 words

[1] Sacks, HS et al. Meta-analyses of randomized controlled trials. N Eng; J Med 1987 Feb 19; 316 (8): 450-5.

exclusive of the abstract, tables, figures, and references. Give explicit details of the method of literature search and use **systematic reviews** or **meta-analysis** when appropriate."

APPLICATIONS IN THE MEDICAL DEVICE INDUSTRY

Meta-analysis is also beginning to have greater applicability within the medical device industry. Given the focus on evidence-based medicine by health care organizations and third-party payers, it is vital that device makers show clinical efficacy or superiority in the best way possible so as to construct a persuasive body of evidence towards reimbursement, as reimbursement can serve as either a driver for—or impediment to—technology adoption.
Legislative changes also can affect the use of meta-analysis and statistical techniques for device adoption. For those products with an extensive history of use, meta-analysis can be useful for updating technical files, especially in those instances in which the number of indications for a product have increased.

A hotbed for device innovation and site of some of the best healthcare facilities in the United States, the state of Massachusetts has recently enacted legislation that places stringent restrictions on the gifts that device makers can give to clinicians. Any gift over $50 must be publically disclosed, with gifts being defined as, "any fee, payment, subsidy, or economic benefit." These strict controls also could reduce the emphasis on relationships to drive device use and adoption.

As the significance of the relationship among companies, their sales representatives, and healthcare facilities is reduced, manufactures will have to rely on other methods to promote the adoption of a new device or associated therapy. Meta-analysis will be one of the most useful methods to support the use of a product or methodology as it incorporates a rigorous, compelling body of evidence.

THE DOWNSIDE OF META-ANALYSIS

Meta-analyses, however, are not perfect. Clear answers are difficult to obtain, and the combined analysis is only as good as the studies used to create it. Publication bias is a serious risk for the unwary business considering investing in a meta-analysis. Often, journal articles are written to promote a particular outcome, and articles that do not support the desired outcome often go unpublished. In addition, research is often sponsored by industry, and the sponsor will not allow negative outcomes to be published.

To overcome publication bias, businesses should seek a neutral party with no vested interested in the outcome of the research to gather the desired research. Although it is tempting to use an in-house employee, a meta-analysis should never be undertaken by someone affiliated with the business, as this casts doubt on the objectivity of the finished report.

ESTABLISHING CRITERIA

Another concern related to objectivity is to establish criteria for the inclusion or exclusion of research. The neutral party gathering and subsequently analyzing the data for the meta-analysis should be given clear guidelines as to how to decide whether to include or exclude each article found. Some considerations include:

— Was the article published in a peer-reviewed journal? Peer-reviewed journals avoid errors in fact by allowing colleagues to edit, comment on, and ultimately approve articles prior to publication.
— Is the article independent research, or is it a review of several articles? For a meta-analysis, it is dangerous to pool data that has already been gathered from multiple sources.
— How many articles have been included from this source? As some companies tend to use journal articles to promote their products, it is important to not bias the results with the overuse of a single source.
— Is the full-text article in English? When including articles, it is necessary to collect the raw data from tables and charts, not the data conclusions found in the abstract, because if the article is not written in English, errors in fact can result.
— How many patients were involved in the study? If the article includes fewer than five patients, it is considered a case report, and should be excluded. Case reports are often unique instances that are not applicable to the product as a whole.

ENSURING ACCURACY AND RIGOR

Before a meta-analysis is performed, either as a stand-alone proposition or as part of a systemic review, the following measures should be incorporated to ensure a high degree of accuracy and rigor:

— **The research question must be defined.** If the question is too wide-ranging—for example the efficacy of a single treatment but for multiple clinical indications—the end result will be a few minimally accurate conclusions drawn from a needlessly vast quantity of data.
— **Inclusion/exclusion criteria must be determined.** An agreed upon set of standards and criteria for each study, e.g. minimum of 10 patients with no individual case studies, is needed to provide as much consistency as is possible when looking at an array of dissimilar studies.
— **Creation of a reproducible protocol that can identify studies from all available databases and resources.** It is critical that as many studies as possible be found that address the research question and meet the inclusion criteria. Not only does this increase the veracity of the meta-analysis by way of a larger and more complete number of data points, it also reduces publication bias.
— **Be aware of bias.** To help reduce bias, data should be collected by at least two authors independently and a data collection form should be used. Standardizing the collected data will help when it comes time to conduct the final meta-analysis.

Bias can also be controlled to a certain degree by using objective third parties such as Nerac to perform the meta-analysis. A funnel plot can be used to help detect the existence of publication bias, especially with a large number of trials, but when data is limited to only a few small studies caution must be exercised.[2]

OBSERVATIONS & CONCLUSIONS

Meta-analysis can be a useful methodology, but only if performed correctly. Recently, a Fortune 500 medical device maker saw its shares fall by 5 percent solely based on the news that the statistical analysis of the clinical data used to show the product's efficacy was flawed. This is a

[2] Egger, M. et al. Bias in meta-analysis detected by a simple graphical test. BMJ, 1997 Sept 13; 315 (7109):629-34.

chilling example that data and statistics must withstand close scrutiny to be considered truly useful. Clinical studies can also be problematic due to confounders or bias. Therefore, it is not unusual for randomized controlled trials to be used as criteria for inclusion.

Once an objective research analyst has been identified to conduct the meta-analysis and all criteria important to the meta-analysis have been clearly established, the analyst will perform an initial search of all available journal databases for relevant articles. This unfiltered result should be shared with the business to determine if a more comprehensive search might be required to find all possible articles. The final list of articles should be at least 40-50 independent research studies, mostly from peer-reviewed sources. When it is possible, unpublished research should be included if it is from reputable sources.
Meta-analysis is an important new tool for the medical device and pharmaceutical industries. As regulations tighten within the FDA and the European Union, validation of safety and efficacy will be scrutinized more closely. Also, when a business wants to promote a new, emergent technology, meta-analysis provides a convenient means of collecting adequate data for researching funding, launch of a new device, or regulatory approval.

Many software products and tools are on the market to assist with meta-data management. Third parties such as Nerac also can perform a meta-analysis, but it is vitally important that these tasks be carried out by individuals familiar with the industry and the technology being analyzed.

ABOUT THE AUTHORS

Denise Ryan brings over 14 years experience as a medical laboratory technician to companies seeking knowledge and analysis in the areas of biotechnology, life sciences, toxicology, and environmental science. Her analytical skills, particularly in the areas of biomedicine and environmental science, help generate information that companies use to make critical business decisions. Before joining Nerac, Ms. Ryan was a medical laboratory technician at Bedford VA Hospital, Waltham Hospital, and Wing Memorial Hospital in Massachusetts and Johnson Memorial Hospital in Stafford Springs, Conn. She also worked in the field of environmental biology for the Massachusetts Department of Environmental Protection's Water Division. Ms. Ryan holds a bachelor's degree in environmental studies from Mount Holyoke College and a master's degree in library science from Simmons College. She is a certified environmental analyst and medical laboratory technician, and she is a member of the Special Libraries Association and the American Society for Clinical Pathology.

Perry De Fazio works with companies in the medical device industry to provide insight about the potential of untapped markets and disruptive technologies. From multi-billion-dollar multinationals to small start-ups, he advises innovators on the development of new technologies and helps vet technologies for license and acquisition. Mr. De Fazio has nine years of industry experience. He was a project engineer at Boston Scientific Corporation, where he led projects at satellite plants and screened new prospective technologies. As an R&D engineer at Tissuelink Medical, he was instrumental in the testing and development of the startup company's first device, which is the platform upon which all of the company's products are based. As a senior engineer at Ortheon Medical, he designed and implemented cadaveric and *in vivo* animal test protocols for a novel soft tissue anchoring system, led projects at satellite plants, and served as the technical expert for several exploratory technology teams. Mr. De Fazio, who holds a bachelor's degree in Biomedical Engineering from Rensselaer Polytechnic Institute, is expert in the areas of technology licensing and development, medical device regulation, patent information science, and competitive technical intelligence. He has specific experience with orthopedic surgery, flexible endoscopy, and tissue ablation.

Deborah Schenberger, Ph.D., brings 16 years of industry and two years of academic experience and insight to medical device companies, particularly those developing implants, to help them to achieve product approval through the FDA, ISO, and CE registration processes. She also analyzes mechanical devices and machines, using her expertise to assess mechanisms for novelty by working across industries to find other applications that may help provide design solutions. Before joining Nerac, Dr. Schenberger was a research scientist and teaching professor in bioengineering at University of the Pacific, where she had earned her bachelor's degree in mechanical engineering years earlier. As a graduate student at the University of California at Davis, where she earned her Ph.D., she studied micro-fabricated sensor development for spinal fusion applications and was a teaching assistant in the Human Anatomy Lab. As part of her dissertation, Dr. Schenberger designed and patented a biomedical sensor for measuring the onset of spinal fusion. Before returning to college, she was an engineering manager at Synvasive Technology, where she designed medical devices for the orthopedic industry. At Ortho Development Corp., she was a product development manager, designing orthopedic implants and instruments. She also spent several years designing mechanical systems with controls for NASA, and later for an entertainment robotics application. She is well-versed in patents and intellectual property, bioinstrumentation, MEMS, biomedical sensors, and nanotechnology. Dr. Schenberger is section chair for the American Society of Mechanical Engineers, and a member of the American Society of Biological and Agricultural Engineers (ASABE), the Biomedical Engineering Society (BMES), and the Institute of Biological Engineering (IBE). She has presented at such forums as the Institute of Biological Engineering Annual Meeting, the 24th Aerospace Mechanisms Symposium at NASA, John F. Kennedy Space Center, and Society of Women Engineers International Conference.

ABOUT NERAC

Nerac Inc. (www.nerac.com) is a global research and advisory firm for companies developing innovative products and technologies. Nerac Analysts deliver custom assessments of product and technology development opportunities, competitor intelligence, intellectual property strategies, and compliance requirements through a proven blended approach to custom analysis: review of technical knowledge, investigation of intellectual property, and appraisal of business impacts. Nerac deploys analysts in diverse disciplines to help clients discover new applications, serving as a catalyst for new thinking and creative approaches to business problems or identifying strategic growth opportunities.