Integrating Economic Analysis into NIH Funded Research

Health Economics Common Fund

National Institutes of Health

SEPTEMBER 11, 2012, WEB CONFERENCE

Executive Summary

The NIH Common Fund

Introduction

The Health Economics program[1] is one of several trans-National Institutes of Health (NIH) programs of research funded through the Common Fund.[2] These programs are envisioned to be transformative, cross-cutting, unique, synergistic, and catalytic. Economics research is highly relevant to the NIH mission as a way of assessing and enhancing the value of NIH investments in research for health care. The focus of the webinar—incorporating economic analyses into clinical research—is one way to enhance the value of the research.

The purpose of the webinar, *Integrating Economic Analysis into NIH Funded Research*, was to encourage collaboration between biobehavioral investigators and economists so that clinical trials and other studies are designed to promote appropriate and prompt implementation of effective and efficacious interventions. Incorporating health economics expertise on the effects of financial and organizational incentives and constraints on the behavior of various stakeholders (including private research and development companies, health care provider organizations, and patients) can expedite implementation of clinical, behavioral, and organizational interventions that have been shown in experimental or clinical settings to be effective in promoting health and wellbeing. The featured webinar participants shared an example of a clinical trial to which economic analyses were added. They then explored the value of incorporating an economic perspective from the inception of clinical study design.

More than 400 individuals registered for the webinar, and more than 200 participated. The participants included researchers, economists, clinical personnel, government staff, and others.

A Randomized Controlled Trial of Depression Care for Acute Coronary Syndrome Patients: Mortality and Major Cardiac Event Outcomes

Karina W. Davidson, PhD, Columbia University

Depressive symptoms are an established predictor of mortality and major adverse cardiac events in patients with acute coronary syndrome (ACS). Davidson and colleagues conducted the Coronary Psychosocial Evaluation Studies (COPES) randomized controlled trial (RCT) to determine the acceptability and efficacy of enhanced depression treatment in patients with ACS.

Depression leads to increased risk of ACS recurrence and mortality, independent of traditional risk factors. Depression predicts reduced long-term survival up to 5 years in post-ACS patients, is dose-dependent, and is highly prevalent in patients. Up to 45 percent of patients have elevated depressive symptoms, and up to 20 percent of these meet criteria for major depressive disorder. Measures of depressive symptoms taken at the time of ACS indicate a 1.79

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[1] http://commonfund.nih.gov/healtheconomics/
[2] http://commonfund.nih.gov/index.aspx

hazard ratio of risk for major adverse cardiovascular events; however, if measured 3 months later, the prognostic risk is raised to 2.25. Unlike most previous epidemiological research that measures a one-time snapshot of depressive symptoms or major depressive disorder, this study included measures across time. The trial design also was informed by previous findings of patient preferences for medication versus counseling.

The COPES trial was designed to explore a depression intervention with patient satisfaction and depressive symptom reduction as primary outcome measures. The design compared a patient preference stepped care model, where steps included either problem solving and/or antidepressant medication, as compared to usual care in patients with ACS and acute depressive symptoms. Patients with continued depressive symptoms after a period of watchful waiting following an ACS event were randomized into the stepped care intervention group or the usual care group.

The results of the trial indicate that the intervention arm was successful in improving patient satisfaction with depression care. The overall change in depressive symptom scores between the usual care and intervention groups was 3.8, and the effect size at 6 months was 0.59, which remained robust at 18 months (0.57). In summary, enhanced depression care for patients with ACS was associated with greater satisfaction, a greater reduction in depressive symptoms, and a promising improvement in prognosis.[3]

Cost-effectiveness of Enhanced Depression Care for Patients with Acute Coronary Syndrome

Joseph A. Ladapo, MD, PhD, New York University

Coronary heart disease is one of the leading causes of death, and depression magnifies the risk significantly. A health economic evaluation is valuable to the COPES trial because of the overall burden of disease and because cost-effectiveness can (and sometimes does) influence decision-making. The team's approach to estimating cost-effectiveness focused on economic costs and quality adjusted life years (QALYs) as measured by the 12-Item Short Form Health Survey (SF-12).

QALYs are one of the most commonly used metrics in cost-effectiveness analysis for measuring effectiveness. QALYs integrate quality and quantity of life with health utility measured on a zero to one scale where one is perfect health and zero is death. The product of utility and duration is the QALY. The ratio between the difference of the cost and the effects, or the cost-effectiveness ratio, was calculated.

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[3] Davidson, K. W., Rieckmann, N., Clemow, L., Schwartz, J. E., Shimbo, D., & Medina, V. et al. (2010). Enhanced depression care for acute coronary syndrome patients with persistent depressive symptoms: Coronary Psychosocial Evaluation Studies (COPES) randomized controlled trial. *Archives of Internal Medicine, 170*, 600-608. doi: 10.1001/archinternmed.2010.29.

For the purpose of this evaluation, economic costs included resource utilization and opportunity costs. Three categories of costs were shared in common between the intervention and usual care arms in the COPES study: outpatient care visits, hospitalizations, and medications. Costs for mental health visits and other components of enhanced depression care were attributed to the intervention arm only. Medicare reimbursement rates and an average wholesale price listing for antidepressant medications were used to estimate the cost of each of these components. The participants were not part of a closed health care system, so it is possible that some sources of health care utilization were missed. Other data limitations included incomplete data on outpatient care, hospitalizations not related to the patients' ACS, and lack of inclusion of other types of economic costs such as out-of-pocket expenses, time costs for participants' travel and waiting, and employment or productivity changes.

A difference-in-differences approach was used to look at the within-group differences and differences between the baseline and follow-up outcomes values. Bootstrapping, which is an approach that resamples from the original data and simulates the population distribution for the cost-effectiveness ratio, was used with patient-level data to estimate confidence intervals.

The SF-12 is stratified into a physical component score and a mental health component score. There was a statistically significant difference in physical component scores between the intervention and usual care groups at 6 months. Overall, the 6-month difference in health utility between the intervention and usual care groups was not significant at the 5 percent level. The overall costs for the usual care group were significantly higher than for the intervention group, primarily because of significantly higher hospitalization costs. On average, the intervention was cost saving by about $600 for patients and improved QALYs by 0.2.[4]

Economic Analysis and NIH Clinical Research
Richard G. Frank, PhD, Harvard University

Economic evaluation methods such as cost-effectiveness analysis are increasingly becoming a part of clinical trial research. The purpose of such analysis is to offer evidence on whether a new treatment is likely to be efficient, in other words, to improve the value of health care treatments. These types of evaluations provide part of an answer to a larger question. The larger question—a translational or policy evaluation question—asks if introducing a particular intervention into practice results in improved use of resources or better value for health care dollars. Typically, clinical trials only provide part of the answer to the larger question, and it is possible they could be designed in such a way as to provide more information to answer this overarching question.

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[4] Ladapo, J. A., Shaffer, J. A., Fang, Y., Ye, S., & Davidson, K. W. (2012). Cost-effectiveness of enhanced depression care after acute coronary syndrome: Results from the Coronary Psychosocial Evaluation Studies randomized controlled trial. *Archives of Internal Medicine*, doi: 10.1001/archinternmed.2012.4448.

A cost-effectiveness analysis embedded in a clinical trial answers a specialized question—it tells us about the potential that a particular intervention has to make efficient use of resources if it is used by the types of people included in the trial and administered with fidelity according to the protocol used in the trial. However, in practice, there are often differences in results between a clinical trial and in the real world primarily because the patients do not have the same characteristics and the administration of the intervention varies in the real world.

The challenge in moving beyond the narrow conception of cost-effectiveness analysis in clinical trials is to design a trial that produces information useful to real-world practice. Several information-gathering strategies can be useful for translating efficiency from the trial environment to the real-world environment: (1) identify which segments of the population are willing to engage in a particular type of treatment (e.g., assess patient preference for medication versus therapy in the COPES trial); (2) examine the heterogeneity of impacts for a particular population of patients (i.e., who benefits the most, which identifiable segments of the population have the best incremental cost-effectiveness ratios); (3) determine the active ingredients of an intervention to identify which components are critical and which are less important in real practice; and (4) designs aimed at multiple chronic conditions should not measure cost-effectiveness results on individual illness components.

The implication of addressing these types of information in a trial is a larger, more expensive trial. Trials will need broader inclusion criteria and more arms. Dismantling components of an intervention in particular requires having a very detailed stratification hypothesis about how the ingredients fit together. Pre-randomization data collection may be more extensive.

Speaker Discussion

Karina W. Davidson, PhD, Columbia University
Joseph A. Ladapo, MD, PhD, New York University
Richard G. Frank, PhD, Harvard University

The three invited speakers engaged in a discussion of considerations for designing a new trial that incorporates economic evaluations while keeping in mind the goals and implications described by Dr. Frank.

Pre-randomization Data Collection Strategies

The speakers identified the need to balance access to detailed historical data about patients in the target population and obtaining the most representative sample. Obtaining detailed personal histories about patients prior to randomization in order to identify characteristics of those likely to accept randomization and/or those likely to benefit most from intervention is not typically done in a clinical trial. It is possible that the growth in use of electronic health records will facilitate this type of data collection in the future. Focusing on populations in

Medicare, Medicaid, Veterans Affairs, or a large closed health system (e.g., Kaiser Permanente, Geisinger) can facilitate obtaining detailed health histories. However, there is a trade off between focusing on particular populations due to access to information versus maximizing the representativeness of the sample.

An ideal approach would be to work with a health care system where there is a lot of confidence about capturing important sources of health care utilization without sacrificing too much generalizability. Rigorously evaluating whether a particular health care system would be an impediment to estimating health care costs that would be generalizable on a case-by-case basis is a reasonable approach.

Several years ago, multiple extraordinarily well-designed trials demonstrated that diverting patients who present themselves for inpatient mental health care to partial hospitalization programs saves money while maintaining equal outcomes. Policies were implemented and Medicare reimbursement regulations were changed based on these results. However, upon implementing the program in the real world, it was discovered that only a very small portion of the patients who used the service would have ever been hospitalized—meaning that it was a different population using the treatment. The treatment ended up costing more and the outcomes were no different. A failure such as this could be avoided, in part, by better understanding the subgroups and how an intervention will or will not work for them in the real world. Heterogeneity of patient preferences and treatment response in the real world needs to be considered and examined.

Dismantling Studies

The speakers discussed the circumstances under which dismantling an intervention to ascertain the active components would be advantageous. If the best component within a complex intervention does not work or if the intervention is not cost-effective, then dismantling might not be useful. In the COPES trial, patient preference was thought by the patients to be important, and it is difficult to think about how to dismantle the other components of the intervention from patient preference. The intervention involves ascertaining patient preference for medication versus psychotherapy and the step intervention. It would be difficult to dismantle psychotherapy versus medication use without removing patient choice.

Multiple Perspectives

Classic cost-effectiveness analysis is to consider the societal perspective (i.e., if something is socially efficient, then it is worth doing) but does not typically consider cost shifting or who bears what costs. The speakers discussed the kind of data that would need to be available from a behavioral clinical trial that would give health economics researchers the confidence that an intervention is, in fact, ready for a demonstration (i.e., to make the "business case" for proceeding). Interventions may be found to be socially efficient in the course of a trial; however, implementation might be limited if the costs were imposed on private payers (e.g.,

medication adherence programs shown to be effective for patients but costly for payers). Presenting results and impacts from multiple perspectives is one way to provide the cost-effectiveness data to incorporate the impacts to society, payers, providers, and patients. Understanding the impacts of an intervention on multiple perspectives has great bearing on translation and implementation of interventions within real-world health care systems.

Double Counting Costs

Methods for incorporating productivity costs in cost-effectiveness analysis continue to be openly debated. The Panel on Cost-effectiveness in Health and Medicine[5] generally recommends not including productivity costs, but to include other sources of data that could be considered related to productivity, such as waiting time. Productivity costs are difficult to measure, and there is not a universally accepted approach to estimating the value of productivity. This is an issue of which health economists need to be aware. However, individual research teams should make the determination about including productivity costs based on the research questions of the particular trial.

Power Analysis

Focusing on economic outcomes increases the power requirements for a trial. Most clinical trials are underpowered for evaluating economic outcomes because cost data tend to be skewed right. Additionally, if subgroups are to be analyzed, even more power is required.

Questions from the Audience

How do you decide what cost is appropriate to assign? What is the benefit of using a Medicare cost versus a cost for a specific institution?

Assigning costs can be a trade off. Medicare costs are thought to be more generalizable than other potential cost estimates, and that is the reason behind the approach taken in the COPES example. Other approaches include capitalizing on the site-to-site variability in costs using hospital accounting systems, if available, or to use hospital charges and cost-to-charge ratios. The overarching goal is to capture resource utilization and analysts should think about the best approach to estimating costs.

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[5] Weinstein, M. C., Siegel, J. E., Gold, M. R., Kamlet, M. S., & Russell, L. B. (1996). Recommendations of the Panel on Cost-effectiveness in Health and Medicine. *Journal of American Medical Association, 276*, 1253-1258. doi: 10.1011/jama.1996.03540150055031.

When is it appropriate within the development of an intervention to do a cost-effectiveness analysis?

Cost-effectiveness analysis information is most useful when it is being used to persuade someone—a policy maker or other decision maker—to adopt a particular intervention into practice. The cost-effectiveness analysis should be tied to the intervention when it is advanced enough that the researchers know what it is going to look like in the real world.

There can be many challenges in collecting cost data. It was recommended that clinical trialists work with health economists early enough in the design of a definitive trial in order to identify all the data that need to be collected well in advance.

What are the basic strengths and weaknesses of using quality of life measures for these analyses? What are the alternative ways to measure quality?

The most frequently used instruments to measure health utility or quality of life are the SF-12, 36-Item Short Form Health Survey (SF-36), the EuroQol 5 Dimension (EQ-5D), and the Health Utilities Index (HUI). Each of these instruments has research demonstrating how to translate responses, and each is validated on different populations. Each instrument has its limitations, which should be weighed against the generalizability and usefulness of the measure.

Can you give advice about working collaboratively with economists?

A good health economist collaborator would be someone who has scientific interests and technical expertise that complement the focus of the clinical trial as well as an understanding of the health care delivery and reimbursement systems.

Where can health economists find information about upcoming trials?

A primary source is http://www.clinicaltrials.gov. All trialists are required to register trials with full protocol information in the analyses prior to randomizing the first patient. A user can enter search terms (e.g., acute coronary syndrome AND depression), and a host of information is returned including start dates, locations, primary and secondary outcome measures, eligibility criteria, and protocols. Another approach is to spend time with the literature to find areas that look promising for adding economic evaluations, possibly where others might not have thought to do so.

Featured Participants

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