AN AUDIENCE WITH…

David Eddy

Founder and Chief Medical Officer Emeritus, Archimedes, San Francisco, California, USA. David Eddy received his M.D. from the University of Virginia, USA, and Ph.D. in applied mathematics from Stanford University, California, USA. For over 30 years, he has made seminal contributions to mathematical modelling, cost-effectiveness analysis, guidelines, and coverage policies. He coined the term 'evidence-based' and developed the original concepts and methods for evidence-based guidelines. In the mid-1990s, he, along with Len Schlessinger, started to develop the Archimedes Model and in 2005 founded Archimedes Inc., a health-care modelling company based in San Francisco.

What factors first inspired you to develop evidence-based methods, and later, mathematical models, for assessing the value of health-care interventions?

From the 1970s to the 1990s, I had been working in an advisory capacity with various organizations that needed to make coverage decisions about new treatments. Before my involvement, decisions were made subjectively by asking experts their opinion. But we introduced the idea that there should be a formal process to ensure that there is good clinical trial evidence to show that the treatment improves health outcomes.

However, this evidence-based approach asks a fairly narrow question: is there good evidence that the treatment or test that is being recommended for coverage, or included in a guideline, is effective? Once a coverage decision has been made, a lot of additional questions arise that extend from the simple question of 'is it effective?' These include: how should it best be used? And: what should we anticipate in terms of the magnitude of its effects on health outcomes such as heart attacks or strokes, and on financial cost? When facing these questions, I was personally frustrated that we were making decisions without quantitatively knowing the effects of treatments or tests on outcomes. So, that led me to think of ways to acquire the desired information.

One way is to conduct more clinical trials. However, if there are ten candidate populations for a drug you can't run a clinical trial in each population. Also, with regards to long-term outcomes, you can't run a clinical trial for 10–30 years as they cost between US$5,000 and $30,000 per person per year. For such questions, mathematical modelling is the only feasible alternative, and is well established in many other fields. We therefore developed the Archimedes model to enable us to get the information we need to make more intelligent decisions in health care.

How can mathematical modelling be applied to drug development?

The Archimedes model can be applied from the Phase II stage of drug development. This clinical phase provides information about how the drug affects physiological variables and biomarkers, such as high-density lipoprotein cholesterol (HDL), and fasting plasma glucose. We can take that information and project through to clinical outcomes, utilization, costs and quality of life. A specific example is a company [undisclosed] that had good Phase II information on six molecules. We analysed the six different compounds along with three different controls and simulated the trial for 10 years. This was done at a tiny fraction of the cost of a real trial, which would have been ~$500 million. In this case, the simulated trial helped them to make decisions about which molecules to pursue and how to design the trials.

Another application is to help select the right target group for a new therapy. We can simulate a wide variety of populations to determine the baseline risk and the effectiveness of the drug in each population. This can help to navigate the trade-off between population size and the likelihood of achieving desired safety and efficacy goals. Also, for each population we can predict how health-care providers would analyse the drug's clinical data if it is approved, and how desirable the drug would be compared with alternatives.

What are the limitations of models such as Archimedes?

Our model will not predict an adverse event for which there is no prior existing evidence, because by necessity the model is based on existing information. So, for example, it would not have predicted the effect of Fen-Phen [a combination of fenfluramine and phentermine that was withdrawn from the market in 1997] on heart valves. However, we can project the potential effect of an adverse event on other outcomes. For example, some of the thiazolidinediones (which modulate the nuclear receptor peroxisome proliferator-activated receptor-γ) cause oedema. This raises the question of what the long-term effect of treatment may be on the development of congestive heart failure. Because there is Phase II trial information on the effect of these drugs on relevant biomarkers, we can project what the long-term outcomes might be.

We do not propose that the model should be used to answer the initial question of whether or not a drug is effective. There has to be at least one good clinical trial showing efficacy of the drug. Once that basic question has been answered with a trial, the model can be used to answer a broad range of other questions that arise when the drug is put into practice. The reason I say that is, even though the model is correct 90–95% of the time, it can be wrong. For example, a model we created on the basis of available medical knowledge suggested that increasing HDL would reduce the incidence of heart attacks. However, the HDL-raising agent torcetrapib didn't reduce heart attacks in Phase III trials for reasons that nobody yet understands.

A key challenge is to get good data. The push towards evidence-based medicine has had the effect of helping ensure that treatments work before we recommend them, but it has also made people alert to gaps in our evidence. In recent years, there has been greater emphasis on collecting evidence, not just in clinical trials, but also in registries and clinical information systems. Furthermore, there are efforts in the pharmaceutical industry to make person-specific data from clinical trials more accessible, particularly for the development of models. As the data improve, we will be able to cover a wider range of conditions and to delve deeper into the underlying molecular pathways that affect disease progression.

Interview by Bethan Hughes