Historical advances in medicine that did not need (or want) a randomized clinical trial.

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#### Abstract

Understanding when randomized clinical trials (RCTs) are needed comes from first knowing when those RCTs are not needed. There are many settings where major improvements in health care came through the use of observational studies. Observational studies have some strengths, such as greater ecologic validity and the ability to study larger populations over longer periods of time, but they have many weaknesses and require much more effort to eliminate other possible causal explanation. Some examples of the triumphs of observational research are establishment of a causal association between cigarette smoking and lung cancer, identification of most of the well-known risk factors for heart disease, and discovery of the link between aspirin and Reye’s syndrome. The work was not easy; but the careful and methodical approach offers a lesson in how to assemble information from a series of less than perfect observational studies to produce a definitive conclusion. These examples help to teach students to recognize when the ethical and logistical challenges associated with RCTs are so great that observational studies, with all their limitations, are preferable.

#### Introduction

In October 2015, health experts in Brazil noticed a sharp increase in the number of cases of microcephaly. This tragic event, where children are born with unusually small head circumferences and severe developmental disabilities, seemed to be geographically associated with the concurrent spread of a new virus, Zika. In response, researchers initiated a host of research studies. Among these were a prospective cohort study of 345 pregnant women in Rio de Janiero who exhibited symptoms associated with Zika infection (Brasil et al. (2016)), a case series of 24 infants diagnosed with congenital Zika syndrome at birth and followed for the next two years of their lives (Alves et al. (2018)), a case-control study of 32 infants born with microcephaly compared to 62 normal births matched by time of delivery and location of residence (Araujo et al. (2016)), among many others. Researchers utilized a wide range of surveillance systems and registries (Lowe et al. (2018)).

What was lacking in all the research studies utilized in the war against Zika, was the randomized control trial (RCT). An informal Pubmed search on the terms “Zika” and “microcephaly” yielded 1,716 publications, but when you click on the link to the right that limits your search to clinical trials, the list dwindles to a single citation that on closer examination is actually a cohort study.

It is not at all surprising that no RCTs were utilized in this investigation. What is surprising, at least to some, is how much was learned so quickly utilizing a range of research methodologies that are commonly held to be inferior to the RCT. In a few short years, researchers were able to track the spread of the Zika virus, identify the modes of transmission, provide a causal link between Zika infection during pregnancy and microcephaly, and characterize in great detail the impact of this condition on early childhood development.

If you want to understand the benefits of RCTs and when they are needed, you should start by examining the times that they have not been needed. This paper will outline three areas where major progress was made without the benefit of RCTs and discuss what this means for the use of RCTs in research.

#### Cigarette smoking and lung cancer

Perhaps the most commonly cited discovery that did not use RCTs was the research that drew a causal link between cigarette smoking and lung cancer. It is still instructive, however, to review the series of studies that led to the 1964 Surgeon General’s report on smoking and health. Although some evidence appeared earlier, the concern about smoking rose largely from five case-control studies, all published in 1950 (Doll and Hill (1950) , Levin, Goldstein, and Gerhardt (1950), Mills and Porter (1950), Schrek and Baker (1950), Wynder and Graham (1950)). This research approach was very new, but the authors took great pains to control for recall bias and confounding (Gail (1996)).

It took more than these five studies to develop a strong case against smoking, but it also required a different way of thinking about research. The authors of these case-control studies were well aware of the potential problems associated with sampling from cases and controls rather than sampling from the general population. In 1951, however, Jerome Cornfield took these studies and placed them on a rigorous mathematical foundation in his landmark paper on case-control studies (Cornfield (1951)).

Around the same time, researchers set up prospective cohort studies to further investigate the link between smoking and lung cancer (Doll and Hill (1954), Dorn (1959), Hammond and Horn (1958)). These studies were massive (more than 460,000 patients total across the three studies) and followed these patients for multiple years. Needless to say, these studies took much longer to complete, but provided a key piece of additional evidence (Alberg, Shopland, and Cummings (2014)).

The researchers received a lot of criticism, of course, and not just from tobacco interests. R.A. Fisher, perhaps the most prominent statistician of the era, published a series of stinging critiques of the research (Fisher (1959), Ronald A. Fisher (1957a), Ronald A. Fisher (1957b), Fisher (1958)). It is difficult to parse these criticisms. One source (Stolley and Fisher (1991)) attributes it a largely unsupportable explanation rooted in genetics combined with a focus on small details that failed to support a smoking-cancer link while ignoring the totality of the evidence.

The controversy inspired one of the prominent researchers in this area, Sir Austin Bradford Hill, to delineate his nine famous principles for establishing causation (Hill (1965)).

#### Risk factors for cardiovascular disease

While many pharmaceutical and surgical interventions for cardiovascular disease used RCTs, the identification of risk factors for this condition required the use of a large observational cohort, the Framingham Study. This study originally comprised roughly 5,000 men and women in the city of Framingham, Massachusetts between the ages of 30 and 59 with a planned follow-up of 20 years (Dawber, Meadors, and Moore (1951)). It is worth noting that the inclusion of women in this study was, in that era, a rather unusual feature. At the end of twenty years, the study was almost ended, but a private funding effort and a concerted lobbying campaign led to the renewal and expansion of the Framingham study (Mahmood et al. (2014)). This expansion included inclusion of the children of the original participants and eventually the children of those children. Two contemporary cohorts of minority participants were also recruited to reflect the changing demographics of the city (Andersson et al. (2019)).

An early finding of the Framingham study, after the four year follow-up visit (DAWBER, MOORE, and MANN (1957)) established hypertension, obesity, and hypercholesteremia as risk factors for arteriosclerotic heart disease (a composite measure of myocardial infarction, angina pectoris, coronary occlusion, or myocardial fibrosis). In 1964, researchers used the Framingham cohort combined with a second cohort in Albany, New York to establish a link between smoking and cardiovascular disease (Doyle et al. (1964)) and contributed vital information to the 1964 surgeon general’s report. Further work elaborated on the greater importance of the systolic measurement of blood pressure on the risk of heart disease (Kannel, Gordon, and Schwartz (1971)).

The number of findings from the Framingham study goes on and on, but more important than the number of studies is the way that this study changed clinical practice. The Framingham study changed the medical community’s attitudes from the belief that heart disease as something to be treated to the belief that heart disease was something that could be prevented (Mahmood et al. (2014)).

#### Aspirin and Reye’s syndrome

Reye’s syndrome is rare disorder seen mostly in children. It can produce serious intracrainal swelling that can lead to serious neurological damage and possibly death (Glasgow and Middleton (2001)). The disease was not well recognized until the 1970s and was very difficult to characterize accurately (Monto (1999)).

The Centers for Disease Control developed a surveillance system for Reye’s syndrome in 1980 to track the number of cases of Reye’s syndrome in the United States and to collect information from the patient’s family and combine that with laboratory results (Belay et al. (1999)).

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