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Recent controversies on comparative effectiveness research investigations: Challenges, opportunities, and pitfalls

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ABSTRACT

The purpose of comparative effectiveness research (CER) is to improve health outcomes by developing and disseminating evidence-based information about which currently available interventions and practices are most effective for patients. Randomized Controlled Trials (RCT) are the hallmark of scientific proof, and have been used to compare interventions used in variable ways by different clinicians (comparative effectiveness RCTs, CER-RCTs). But such CER-RCTs have at times generated controversy. Usually the background for the CER-RCT is a range of "standard therapy" or "standard of care." This may have been adopted on observational data alone, or pilot data. At times, such prior data may derive from populations that differ from the population in which the widely variable standard approach is being applied. We believe that controversies related to these CER-RCTs result from confusing "accepted" therapies and "rigorously evaluated therapies." We first define evidence-based medicine and consider how well neonatology conforms to that definition. We then contrast the approach of testing new therapies and those already existing and widely adopted, as in CER-RCTs. We next examine a central challenge in incorporating the control arm within CER-RCTs and aspects of the "titrated" trial. We finally briefly consider some ethical issues that have arisen, and discuss the wide range of neonatology practices that could be tested by CER-RCTs or alternative CER-based strategies that might inform practice. Throughout, we emphasize the lack of awareness of the lay community, and indeed many researchers or commentators, in appreciating the wide variation of standard of care. There is a corresponding need to identify the best uses of available resources that

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will lead to the best outcomes for our patients. We conclude that CER-RCTs are an essential methodology in modern neonatology to address many unanswered questions and test unproven therapies in newborn care.

Evidence and standard clinical practice

In recent decades, clinical experts have embraced the goal to provide "evidence" to guide medical practice and research. Evidence-Based Medicine (EBM) has become the guiding force in clinical practice and is now mandatory in the opinion of professional societies and clinical leaders. One pioneer of clinical epidemiology and EBM—David Sackett—explicitly linked the practicing clinician, the individual patient, and research into a continuum:

> Evidence-based medicine, whose philosophical origins extend back to mid-19th century Paris and earlier, is the conscientious, explicit, and judicious use of current best evidence in making decisions about the care of individual patients. The practice of evidence-based medicine means integrating individual clinical expertise with the best available external clinical evidence from systematic research.[1]

Sackett's broad vision of EBM is an inspiring definition of health care standard practices. This approach explicitly embraces the individual patient and her/his preferences. Admittedly, how standards of care are defined, and the levels of evidence supporting commonly used practices, vary. Although the terms "standard practice," "standard therapy," and "standard of care" are by some interpreted to have subtle and meaningful distinctions, we will use them interchangeably in our discussions.

Commonly used standard-of-care practices can be based on very little evidence. They may also be affected by non-scientific considerations, such as potential legal concerns regarding harm and responsibility.[2] However, recent approaches to adoption of new therapies into standard practice, nowadays, may emphasize the degree of evidential-scientific rigor.[3] Such an approach bases itself explicitly on the evidence-based pyramid and prioritizes randomized evidence. In fact some go as to argue that in the absence of RCTs there is no standard of care.[4]

However, as neonatologists, we are forced to grapple with a somber reality. This is the reality of a low number of RCTs in the neonatal population.[5]

For example, in one specific area there has been an excellent process to develop guidelines for care, of newborn, by the International Liaison Committee on Resuscitation (ILCOR). The recommendations by ILCOR for newborn infants rests currently, on a poor level evidence. Less than 15% of recommendations were based on RCT data, and a full 75% of recommendations either had no controls or were extrapolated from other populations animals, (animals, or mechanical models).[6] Yet neonatal resuscitation is an area where many existing interventions could be compared in CER studies to advance the field. The same need occurs in almost every area of neonatal practice where there are many existing interventions that need to be compared.

Currently many standards of care are established without rigorous prior evidence. Without new evidence from traditional RCTs becoming available, clinicians are often forced to create new "standards of care." For example, in the case of blood transfusions, the advent of "new" blood-related infections such as HIV,[7] or the entity labeled as Transfusion Associated NEC,[8] have influenced practice toward less transfusions. In addition, randomized trials in adult and pediatric critical care (at best only indirect evidence for neonatal care) suggested added risk with liberal transfusion guidelines, which also encouraged lower hemoglobin and hematocrit.[9,10] This background may have influenced at least some neonatal centers to adopt stricter transfusion guidelines on the basis of inferred risk.

In another example, oxygen radical disease was increasingly implicated in the etiology of many diseases of the preterm beyond the already recognized retinopathy of prematurity. This had already persuaded some centers to adopt strategies to limit supplemental oxygen exposure even in the absence of RCT data.[11] Other stimuli for changing care in the absence of significant new evidence, include rising recognition of the risk:benefit ratio of some therapies and of the need to consider health care costs.[12] This is so especially with new expensive technologies.[13] In effect, these patterns confirm that standards of care, are not necessarily eternal and may warrant reevaluation by CER-RCTs.

Ideally, changes in standards should be driven by new high-quality evidence. There is little debate that new or innovative therapies must fulfill certain imperatives of rigorous testing to conform to US Food and Drug Administration (FDA) and other agency norms before acceptance into standard of care.[3] However, what is the situation for practices already embraced by clinicians, but based on low levels of evidence? Therapies prescribed in clinical practice are often adopted over time from myriad sources, even if only based on well-intended rationale. In neonatology, for example, many feeding regimens have passed down over the years, as "established." Rarely have these therapies been subject to randomized controlled trial evaluation. While not everything prescribed can be rigorously tested, the number of such evaluations can, and should be, extended. This sentiment has gained support. Concomitantly, interest has grown in evaluating not only ground-breaking "new therapies," but also therapies that are long-standing in the armamentarium. This awareness led to a widely accepted need for "comparative effectiveness research" (CER).

What is comparative effectiveness research?

CER studies were defined by the Institute of Medicine in 2009 as:

> … the generation and synthesis of evidence that compares the benefits and harms of alternative methods to prevent,