

# Challenges and opportunities in comparative effectiveness research

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As comparative effectiveness research (CER) evolves in the coming years, clinicians and policymakers will be well served by CER publications that exemplify state-of-the-art research questions and methods. According to the Institute of Medicine (IOM), the “overall goal of CER is the generation and synthesis of evidence that compares the benefits and harms of alternative methods to prevent, diagnose, treat and monitor a clinical condition, or to improve the delivery of care. The purpose of CER is to assist consumers, clinicians, purchasers, and policy makers to make informed decisions that will improve health care at both the individual and population levels”.<sup>1</sup> To achieve this overall goal, we conceptualize CER as having five specific subgoals:

1. To document performance and extent of variation in outcomes.

When people think of CER, they think of the interventions that must be compared. Prior to developing interventions, however, we must know what the clinical problem is and to what extent it must be addressed. Which outcomes could be improved?

2. To identify sources of variation in outcomes.

After identifying the clinical problem, we need to identify dimensions of variation. How much improvement is likely possible through patient-level interventions, provider-level interventions or system-level interventions? Is the health outcome worse for subgroups of the population, defined demographically (eg, racial or ethnic groups), clinically (eg, for individuals with certain comorbid conditions), or along psychosocial variables (eg, individuals with particular belief systems)?

3. To design and test interventions that address known sources of variation in outcomes.

Once sources of variation have been identified, interventions can be designed to most effectively address the clinical problem in the proper subpopulation. Knowing the sources of variation will guide intervention design, including specifying the appropriate research question and designation of a proper control group to address the research question. This information will also inform intervention content and dosing. Formative research, including qualitative research and pilot studies, can be conducted to help guide these decisions. In larger trials, interventions can then be compared to assess the relative comparativeness. This is the aspect of CER that has received the most attention in recent publications.

4. To identify barriers and facilitators to implementation and maintenance of effective interventions.

Once effective interventions have been identified, research is needed to determine the ease or difficulty with which the intervention can be implemented and

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maintained within a health care system, private practice, insurance company, or other entity. At this stage, the cost-effectiveness can be evaluated. If an intervention is effective but highly resource intensive, implementation may be prohibitive.

#### 5. To translate effective interventions into practice.

The final step in the CER circle is to put into practice effective and cost-effective interventions to improve health outcomes in large patient populations.

Our personal research agendas will be greatly informed by these goals, and *Comparative Effectiveness Research* seeks to publish articles that satisfy one or more of these goals in several general areas. To effectively address these goals, there are evolving debates about research questions, study designs, and reporting of study results that can be informed by rigorous CER.

## Types of questions

First, CER studies will be most useful, as outlined by the IOM, if they go beyond comparing an intervention to usual care or attention control, which has been discussed at some length in prior publications.<sup>2-6</sup> Studies that compare drug/device/behavioral intervention A to drug/device/behavioral intervention B more fully realize CER's promise.

Second, it will be important to understand for whom drug/device/behavioral intervention A works better or less well via moderation analysis. As an excellent example, van Stralen and colleagues examined whether the effect of a tailored physical activity intervention were stronger for individuals of different age or body mass index groups.<sup>7</sup> A particularly timely issue is the lack of evidence on the time in the disease course when self-management may be optimally effective (eg, immediately after diagnosis or later in the disease course). There is a need to determine whether self-management approaches need to be tailored to different age bands and different cultural settings, and should be extended to include caregivers and family members.<sup>8</sup>

Third, CER studies should thoughtfully evaluate the mechanism by which an intervention impacts the primary (and other) outcomes via mediation analysis.<sup>9</sup> An excellent example of a well done mediation analysis is evaluation of whether the use of family/friend and neighborhood resources partially explained the relationship between a Mediterranean Lifestyle program and physical activity and dietary outcomes.<sup>10</sup>

## Types of study designs

There have been important developments in study designs in recent years, which can serve CER well by generating results

that more directly address policy and clinical questions of most interest. *Comparative Effectiveness Research* would welcome manuscripts that discuss the challenges and uses of novel or underused study designs, including practical clinical trials,<sup>11,12</sup> cluster randomized controlled trials,<sup>13,14</sup> sequential multiple assignment randomized trials,<sup>15-17</sup> and randomized controlled trials (RCTs) that are paired with observational studies.<sup>18</sup> We would also welcome papers that examine novel or thoughtful approaches to identifying causal effects from quasi-experimental study designs, such as propensity score methods or instrumental variables methods.

Evaluation of alternative interventions in applied CER studies are welcome from a broad range of well established study design methodologies, including single-site RCTs, multisite RCTs, multinational RCTs, and quasi-experimental studies. In addition to primary studies, systematic reviews can inform CER research. Systematic reviews are typically conducted to estimate the magnitude and direction of an effect and may evaluate potential moderators (eg, to inform tailoring efforts of future interventions) and mediators (eg, to understand the why an intervention had null or positive effects). In addition to addressing these conventional research questions, systematic reviews can be used in identifying key intervention components,<sup>19</sup> optimal dosing, or fidelity.<sup>20</sup>

## Reporting of research

Guidelines for reporting study results have been developed and are endorsed widely. Reports of observational study results should follow the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) statement, which includes checklists for different study designs (ie, cohort, case-control, and cross-sectional).<sup>21</sup> Reports of RCTs should follow the CONSORT (Consolidated Standards of Reporting Trials) statement, which includes a checklist and diagram.<sup>22</sup> Systematic reviews, including meta-analyses, should follow the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement, which also includes a checklist and diagram.<sup>23</sup>

Despite these efforts to encourage more complete reporting of study elements and results, there is still room for improvement. For example, there is little reporting on factors relevant to fidelity, such as actual versus intended dose and content of the intervention.<sup>24</sup> This information could inform translation from the efficacy setting of a carefully controlled RCT to real-world effectiveness or the modification of a nonefficacious intervention into one that has efficacy and effectiveness. To this end, we encourage authors to report on the various components

of intervention dose (frequency, duration, amount, and purity).<sup>25</sup> Authors are also encouraged to report on factors that could moderate intervention fidelity, such as quality of delivery and participant perceptions.

These examples represent a small fraction of the topics and methodologies that we hope will be addressed by CER studies in the coming years, some of which will be published in *Comparative Effectiveness Research*. Greater specificity of the issues outlined above is needed to realize the value of CER via experimentation and publication.

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