

# Comparative Effectiveness and the Future of Clinical Research in Diabetes

Comparative effectiveness research (CER) has a number of features that distinguish it from clinical research in general (1,2). CER is, in essence, framed by asking the core question: for a doctor and a patient, what is the best treatment for that patient in terms of both benefits and harms? To answer that question, the process essentially would require effective translation of the following issues: 1) head-to-head comparisons of the proposed interventions versus the best available alternatives; 2) emphasis on both benefits and harms, the harms often having the most immediate impact on the patients; 3) the examinations of effectiveness in key subgroups within a disease, so that a given patient and doctor can easily match the patient with that group; 4) the study of multiple relevant outcomes, each having adequate power to detect differences; and 5) the impact of the provider, and the differential quality rendered, especially in large multicenter trials. Highlighting these features has given rise to the notion that, in addition to classic randomized controlled trials (RCTs), “pragmatic” trials must be conducted. Further, observational studies carried out through registries or other databases need to be used to detect uncommon but important harms, to provide data on subgroups not included in trials or included in small numbers, and to evaluate the effectiveness of care in community settings. In short, the overarching goal of a comparative effectiveness exercise is to ask a very simple question, “Does an intervention work, and if so, for whom and in what setting?”

In this issue of *Diabetes Care*, the rationale and design of the Glycemia Reduction Approaches in Diabetes: A Comparative Effectiveness Study (GRADE) is published (3). As outlined by the study investigators, GRADE “is a pragmatic clinical trial that will make head-to-head comparisons of major drug classes currently used to treat [type 2 diabetes], with the overarching goal of providing better guidance to practitioners in the choice of medications.” As such, by design, this study will compare the currently available products for treatment of type

2 diabetes, i.e., sulfonylurea, dipeptidyl peptidase 4 inhibitor, glucagon-like peptide 1 receptor agonists, and basal insulin in recently diagnosed, metformin-treated patients. It may be because of timing or the availability or other issues, but at this time it doesn’t appear that a sodium-glucose cotransporter-2 inhibitor will be part of the study. GRADE will examine the effectiveness of the drugs in maintaining goal glycemia (A1C <7%, <53 mmol/mol) over time. Other outcomes reported will include relative effects on selected microvascular complications and cardiovascular risk factors; patient-centered outcomes such as adverse effects, acceptability, and tolerability; and cost-effectiveness.

Given this background, does the GRADE trial match up to the criteria for optimal CER research? Well, the answer is both a “Yes,” and a “No!” A resounding “Yes” with respect to one of the major issues, head-to-head comparisons: It is very difficult for the industry to perform such head-to-head trials for obvious reasons, and with this proposal, the GRADE investigators have taken a further step, bravely, with a four-arm comparison. Thus, just based on this parameter, the study is novel and important. The results will clearly add new knowledge on how best to treat these patients.

On the other hand, GRADE may not be considered a pure CER study. Specifically, one can argue that it does not address, or perhaps does address well enough, the other critical issues. Based on the current design, statements will not be able to be made, without blocking or stratifying, about patients in key subgroups as defined by past evidence by the investigators themselves and by the American Diabetes Association Clinical Practice Recommendations (4). For example, some of these subgroups will include 1) patients with high versus at- or below-target A1C; 2) low socioeconomic status patients and older patients with multiple chronic conditions (particularly cardiovascular disease) (5,6); and 3) those patients with multiple medications (i.e. polypharmacy) (7), because it would appear that the sample size may be

too small for these more complex patients. In addition, without special attention, patients with high BMI, patients with depression, patients whose adherence is less than optimal (8), and other subgroups defined by the variables mentioned by the investigators, will be analyzed only in the post hoc analyses. One very important concept would be the concern that this trial, based on these limitations, could suffer the fate of Look AHEAD (Action for Health in Diabetes), ACCORD (Action to Control Cardiovascular Risk in Diabetes), and ADVANCE (Action in Diabetes and Vascular Disease: Preterax and Diamicon Modified Release [MR] Controlled Evaluation)—all disappointing in not decreasing the occurrence of cardiovascular events, as pointed out in a recent editorial (9). The evaluation for subgroup effects, or heterogeneity of treatment effects, is a critical issue in CER (1,8,10–12).

Both macro- and microvascular outcomes are to be collected. It will be important to ensure that there is adequate power to show differences. Adequate power will be needed even with microalbuminuria because blood pressure treatment may modify its development. Thus, the investigators will need to ensure that these outcomes will provide meaningful information given the number of subjects evaluated for a relatively short timeframe in patients within 5 years of diagnosis. Thus, one would wonder, based on the design, as to whether these long-term outcomes may be problematic.

GRADE might be more appropriately labeled an “efficacy” rather than an “effectiveness” trial. It would appear that the patients are highly selected for adherence. Further, many of the study sites appear to be led by well-established clinician researchers in the field of diabetology and endocrinology. Since the target patient cohort appears to be more appropriate for primary care practice than a subspecialty population, it will be critical for these specialists to work closely with the primary care doctors in their geographical areas.

There is also the issue of patient centeredness, a major feature of the

Patient-Centered Outcomes Research Institute (PCORI) strategies. A tight efficacy trial, focusing intensely on both glycemic control and on side effects, and which could be the basis for larger studies, possibly observational, in real life settings, is badly needed. To explicate the harms, more attention would have to be paid to generic quality of life measures, diabetes-specific quality of life measures, the measurement of mild as well as more serious episodes of hypoglycemia, the measurement of nonadherence due to drug side effects or depression, and satisfaction with treatment. These issues are mentioned in the article, but appear to be secondary, not equal coprimary sets of outcomes. Thus, an issue the investigators need to consider is the possibility that these factors may not be assessed by frequent enough administration of the questionnaires.

In summary, GRADE represents the largest study to date funded by the National Institutes of Health in evaluating management of type 2 diabetes. In this regard, this study is a huge undertaking and is an important next step. Even though GRADE would not be seen as fulfilling many criteria for CER, it can provide, especially with intense attention to adverse effects, the kind of short-term comparative information that providers who care for patients with diabetes so badly need.

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