On Studying Effectiveness

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In this issue of the *Journal*, Kemp and colleagues[1] report a study of the effectiveness of zafirlukast for less-than-optimally controlled asthma in a large number of family practice offices. The project is named ACCEPT (Accolate Clinical Experience and Pharmacoepidemiology Trial). Though interesting enough in terms of content, it is more important to family practice for what it represents: a prospective cohort effectiveness trial.

The prospective cohort study of effectiveness may reasonably be considered the next step in the development of evidence-based primary care practice. The last decade has seen the publication of large-scale randomized controlled trials (RCTs) addressing questions important to family practice. However, these trials have most often addressed efficacy, not effectiveness. Efficacy is a test of a technology: how well an intervention, properly applied under carefully controlled circumstances, *can* work. What matters to family doctors is effectiveness: what benefit an intervention *does* deliver to unselected patients in real-world settings.

The emphasis on intention-to-treat analysis in randomized controlled trials is a significant step toward measuring effectiveness (though trialists still often find it difficult to resist the temptation to report results by treatment received). However, many factors hinder the family doctor's ability to secure the effects demonstrated in RCTs for his or her patients. RCTs commonly screen many patients for every one enrolled. Extensive lists of exclusion criteria are necessary for performing a clean and interpretable RCT, but the family doctor must treat all comers — including the majority that would not qualify for an RCT.

The family physician must also treat patients in the time and with the resources available in a busy practice. The effort and personnel involved in an RCT cannot be replicated in the family physician's office. Patients also have limited time, attention, and resources, and generally will not focus their lives around what is often just one of their several health concerns.

RANDOMIZED CONTROLLED TRIALS AND THE REAL WORLD

The real world of primary care, for all these reasons, is never as clean or as focused as an RCT. How can the family doctor gauge what the number needed to treat (NNT) in her or his practice is likely to be? Some interventions, such as aspirin for patients with coronary artery disease, are quite robust. Patients need not be especially focused on their illness or treatment to use them, and the results are not very sensitive to other health conditions. The family physician can reasonably expect the NNT in the real world to be not too much more than that demonstrated in RCTs. Other interventions are not robust at all. These interventions are very dependent on careful patient selection, and the difference between benefit and harm is quite small. Warfarin anticoagulation for prevention of stroke in patients with atrial fibrillation is an example of a nonrobust intervention. Most practices will serve a significant number of elders at high enough risk for falls, or with other comorbidities, to elevate their risk of major hemorrhage above the risk reduction offered by anticoagulation. Blind reliance on NNTs from published RCTs would lead to harming, not helping, patients with the treatment. Most family doctors are well aware of such limitations, but only in a qualitative sense. Quantifying the issue provides more substantive guidance, and is the standard to which evidence-based family physicians should hold researchers.

PROSPECTIVE COHORT EFFECTIVENESS TRIALS

The prospective cohort study does not replace or replicate the RCT as a demonstration of efficacy, except perhaps for those few interventions with large effect sizes and low potential for bias, where the more rigorous controls of the RCT are not necessary to forestall false-positive findings. Rather, the prospective cohort study, exemplified by ACCEPT, offers the kind of quantified effectiveness evidence the family physician needs to determine the robustness and practicality of an intervention.

ACCEPT illustrates some of the key features of a prospective cohort effectiveness trial, and also some of its weaknesses. One important feature is the enrollment of patients. ACCEPT was performed in more than 900 sites, with approximately 5 patients at each site. For statistical reasons, that is enormously advantageous;— indeed, almost a necessity. That fact raises a significant issue for family practice: To generate the kind of information we need in practice, many of us must host research in our practices. The old model of research being performed in major centers and diffused out to community practice will no longer suffice.

ACCEPT was done in a network of physician practices assembled specifically for that purpose. Though that is practical for some projects, as a general principle it is a costly way to conduct research. It also necessarily limits the interpretation and generalizability of the results. A practice-based research network (PBRN) can be much better characterized, as the cost of studying the network itself can be spread across many studies. An

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existing PBRN can also perform such studies without the recruitment overhead of assembling an ad hoc network. However, the PBRN must carry the overhead of maintaing itself between studies, and therefore, must stay busy enough to cover its infrastructure costs. The PBRN can, however, serve as an instrument to attract public and private funding, broadening the base of support for prospective cohort studies.

Another limitation of ACCEPT is the absence of a rigorous control group. The investigators do not attempt to prove zafirlukast superior to placebo. That has already been done in other studies, and the RCT is the proper methodology for doing so. ACCEPT did limit its enrollees to those with at least moderate symptoms (because the researchers wanted to address only those patients who needed a change in therapy; they did not try to change the therapy of stable patients). Of course, some patients with moderate symptoms are mild asthma patients who are simply in a bad phase, and will regress to their baseline. The results seen in this study, therefore, may be a bit optimistic, and this is another weak point of ACCEPT. In general, the prospective cohort effectiveness study should condition participation on as few selection criteria as possible. Though rigorous control groups are not necessary, it is desirable to include some sort of comparison group to estimate how much of the effect observed may be regression to the mean, secular trend, and so forth.

EFFICACIOUSNESS OR EFFECTIVENESS?

ACCEPT demonstrated that family practice patients like ours would take zafirlukast, and that they would realize benefits similar to those found in RCTs. That is reassuring, but some prospective cohort studies will be done that do not find the anticipated benefits. Some interventions will be proved *efficacious* in RCTs but not *effective* in real-world family practice. What will we make of such studies? There will be great temptation to believe that the RCTs were correct, and the prospective cohort study simply failed to find the benefit that was really there. Perhaps the study was not large enough, or included too many of the wrong kind of patient. Surely these arguments will be raised by advocates of the study intervention. It will be important for family physicians to stick to their scientific guns when this occurs. Our patients require real, not theoretical, benefits. Interventions that do not hold up in primary care practice, or that offer effects so weak they are not detectable, are not worth our patients' time and effort. It will be our responsibility to determine which interventions to use and which to ignore, despite any outside pressure.

ACCEPT was funded by the manufacturer of the study drug. It was clearly in the manufacturer's interest to do so, for several reasons. Getting more than 900 practices to prescribe a medication, enhanced by the respectability of research, is good marketing. Demonstrating real-world results is as important to manufacturers as it is to family physicians. Such a consonance of interests is a happy circumstance, and illustrates a useful model of industry-sponsored primary care research. But there are many interventions that family doctors need to test that are not of particular interest to manufacturers. The greatest benefit from the prospective cohort study methodology will be derived when family physicians convince funding agencies, both public and private, of the need to support this type of research. For that to occur, the methods and determinants of quality in prospective cohort effectiveness trials must be carefully determined and disseminated. Family practice as a specialty has been building expertise in clinical epidemiology and research methods. The prospective cohort effectiveness study is a perfect match for that growing expertise.