My colleague and I, who work in the area of observational research, used to say that Phase III clinical trials are hypothesis confirming, in that hypotheses for these trials are established \textit{a priori} and then used to generated data to either confirm or refute the hypothesis.

Observational research on the other hand is hypothesis generating, leveraging study data to generate likely hypotheses during or even after data collection. But I wonder if we had it all wrong all along? While regulators are insistent upon Phase III data for product approval, aren’t we then really using post-approval observational research to confirm how these products stack up in the real world?
Real-world data analysis is at the heart of observational research and comparative effectiveness research (CER). While much has been written on the subject, I can’t help but feel that one day soon, the evidence needs will surely become clear, and drug developers will at last have clarity of CER expectations and regulators will be harmonious in their approach to the subject. But in the meantime, it feels as if the road to CER clarity is long and one can’t help but ask, “Are we there yet?”

Messner, Towse, Mohr and Garau¹ ponder the future of CER globally in “The future of comparative effectiveness and relative efficacy of drugs: an international perspective.” Seeking to predict what the international drug development environment might look like, across primarily the US and Europe in 2020, the authors then seek to determine what type of CER (in the US) and Relative Effectiveness (RE in the EU) will be needed. By using initial interviews with thought leaders followed by more in-depth Delphi panels, the authors construct scenarios and expectations for CER and RE of new drugs in 2020. Their results are summarized below:

Table 1. Essential elements the US and EU ‘most likely’ scenarios

<table>
<thead>
<tr>
<th>US ‘MOST LIKELY’ SCENARIO</th>
<th>EU ‘MOST LIKELY’ SCENARIO</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Mixed health delivery system, but patients in integrated health systems have doubled</td>
<td>• Regulatory change: PAESs are introduced</td>
</tr>
<tr>
<td>• Electronic Health Record (EHR) interoperability between a few large players or states; but many patients still not captured in EHRs</td>
<td>• Convergence of methods for relative effectiveness assessment; but reimbursement decisions still made nationally</td>
</tr>
<tr>
<td>• Data mining opportunities using large mixed data sources product few new insights</td>
<td>• Ability of HTA bodies to request post-launch studies of their own is constrained by regulatory PAES role</td>
</tr>
<tr>
<td>• Growing high-quality infrastructure for distributed database networks (PCORI, Networks, Sentinel)</td>
<td>• Regulatory and HTA bodies coordination prelaunch by not post-launch</td>
</tr>
<tr>
<td>• Highly active patient groups participating in distributed networks and other activities</td>
<td>• Increased use of disease registries in some countries and progress in EHRs; some development in non-experimental methods but limited increase in acceptability to payers</td>
</tr>
<tr>
<td>• Can embed clinical trials within registries (especially in the rare disease space)</td>
<td>• Industry responsible for financing and conducting studies</td>
</tr>
</tbody>
</table>

¹ J. Comp. Eff. Res. (Epub ahead of print)
In the US system, one might summarize that the immediate promises of Big Data appear to be waning. And while conducting CER in closed, fully integrated systems, such as Kaiser, may grow; EHR still has a long way to go to capture sufficient patient data to make it completely generalizable. In the US, it appears that substantial opportunities remain in traditional, prospective CER, either through purely observational research or through Pragmatic Clinical Trials (PCTs) with a simple element of upfront randomization. And while both Sponsors and Contract Research Organizations (CROs) will continue to push the boundaries of database research, the need for professionals well-versed in traditional experimental approaches is still greatly needed.

In Europe, the advent of Post-Authorization Efficacy Studies (PAES) as a way for regulators to mandate post-approval studies of product effectiveness, could alter the once dominant power of Health Technology Assessment (HTA) Committees. Unlike the US where coverage and reimbursement decisions are made at the payer level, it appears that EU bodies will be looking squarely at Sponsors to provide the evidence data needed for national-level approvals. Also in the EU, non-experimental data do not appear to generate the same level of acceptance as traditional experimental approaches, which may further diminish the apparent usefulness of observational research data to key decision-makers. In total, the landscape in the EU seems to show a shift of power from the HTA Committees back to the Regulators, with Sponsors being forced by regulatory mandate to provide RE evidence. Sponsors and CROs therefore would be wise to cultivate these regulatory relationships, thoroughly understand the RE evidence requirements set by past product approvals, and factor in PAES into post-approval study budgets.

So no…we’re not there yet. But as long as inherent differences exist between regulatory and payer needs, healthcare financing remains a limited entity, and patients continue to educate themselves in their own care and inherent benefits/risks of treatments, we’ll continue down the path of evolving CER. The path diverges a little, depending on globality, but the destination is the same: Better data for better decision making for better outcomes at better costs.

Peggy Schrammel
Vice President,
Portfolio Management and Project Leadership,
PAREXCEL Commercialization
WHEREVER YOUR JOURNEY TAKES YOU, WE’RE CLOSE BY.

CORPORATE HEADQUARTERS
195 West Street
Waltham, MA 02451
USA
+1 781 487 9900

Offices across Europe, Asia and the Americas

www.PAREXEL.com