National Academies Workshop Suggests Principles for Use of Real-World Evidence

By Conor Hale

Experts convened at the National Academies of Sciences, Engineering and Medicine to examine how the uptake of real-world evidence will impact medical product development, recommending producers and consumers of evidence focus on maintaining transparency, accountability and reproducibility of results.

Attendees agreed that, above all, transparency was key. The reasoning behind all design decisions should be clear and available for anyone to look at, they said.

“Are other people able to access this data source and reproduce the work? Or do people have free access to all the transformations that happened between the source dataset and the analytic dataset?” asked workshop series co-chair Greg Simon, a research professor at the University of Washington and head of the Mental Health Research Network.

“I’d make a strong case that for credibility, that’s absolutely foundational,” Simon said, adding that without a study’s code and algorithms being made available for public review, confidence in the scientific findings could falter.

Although, simply posting the algorithms online isn’t always helpful; not everyone has the ability to analyze raw, complex computer code. After trials are thoroughly described — including any adjustments for aspects of variation among respondents in site identification cycle times, indicating “highly inconsistent practices,” the report said. Nearly three in 10 sites were new, with no prior history of working with a sponsor or CRO.

Tufts CSDD senior research fellow Mary Jo Lamberti, who led the analysis, said drugmakers are trying to improve the timeliness of the site initiation process.

Sponsors are investing in technology and working to make contracting and budgeting negotiations — which can be a significant drag on the process — more efficient, Lamberti told CWWeekly.

“It’s happening, but it’s just not happening fast enough,” she said.

see Tufts CSDD on page 5
Industry Briefs

EMA Revises Guidance on Biomarkers for Alzheimer’s Therapies
The EMA’s Committee for Medicinal Products for Human Use revised its guideline on the clinical investigation of treatments for Alzheimer’s disease, focusing on the design and analysis of safety studies and the potential use of biomarkers in various stages of development. The revision, which takes effect on September 1, separates biomarkers according to their potential use: diagnostic, enrichment, prognostic, predictive and pharmacodynamic. The guideline notes that while most biomarkers still require validation for these purposes, cerebrospinal fluid markers, as well as MRI and PET imaging markers, “are qualified for the enrichment of study populations,” even though the biomarkers have not been qualified for use in preclinical Alzheimer’s disease. Identified adverse events should be categorized in relation to the treatment duration, applied dosage, recovery time, different age groups and other variables, the guideline said, and all adverse events occurring during clinical trials should be fully documented with a separate analysis of adverse drug events that lead to drop-outs and fatal outcomes. The revised guideline is available here: www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2018/02/WC500244609.pdf.

NHS Harmonizes CTA Templates Across England, Scotland, Wales and Northern Ireland
A new Model Clinical Trials Agreement from the NHS’ Health Research Authority will allow a single model contract for commercial R&D to be used in England, Scotland, Wales and Northern Ireland, unlike the 2011 nation-specific versions. The revised templates are designed to be used without modification for industry-sponsored trials in patients in hospitals throughout the health service. The Association for the British Pharmaceutical Industry said it hopes the updated agreement, which took effect March 1, will be used by companies and NHS research sites without changes to reduce the time for clinical trial start-up. The HRA expects sites to continue to accept unmodified 2011 versions of the template, while sponsors and CROs finalize their transition to the new version.

FDA to Host Public Meeting on Complex, Innovative Trial Designs
The FDA is holding a public meeting March 20 on the use of complex, innovative clinical trial designs, to inform regulatory decision-making, the development of a pilot program and a guidance document required by the 21st Century Cures Act. The meeting sessions will be held at the FDA’s White Oak campus and will focus on adaptive designs; the use of external or historical control subjects, Bayesian designs and master protocols; and simulations for confirmatory trial design and planning. The meeting will be split into four sessions: Using Prior Data from Early Phase Trials to Inform Phase III Designs; Utilizing Patient Registry and Natural History Study Data to Advance Therapeutic Development for Rare Diseases; Leveraging Master Protocols for Trials with Small Patient Populations; and Additional Topics for Consideration in Rare Disease Settings. The Cures Act directs the FDA to develop guidance addressing the use of complex trial designs, ways sponsors may obtain feedback on technical issues related to simulations, the submission of resulting information, the types of quantitative information that should be submitted for review and recommended analysis methodologies, the agency said. The meeting is also intended to meet a PDUFA VI performance goal. More information can be found here: https://www.fda.gov/Drugs/NewsEvents/ucm598002.htm

Oxford Researchers Identify Discrepancies Between ClinicalTrials.gov and the EUCTR
Approximately one-sixth of clinical trials registered on both ClinicalTrials.gov and the EU Clinical Trials Register have discrepancies in their completion status, according to a study published in PLOS ONE. Researchers from the Evidence-Based Medicine DataLab at the University of Oxford found multiple errors and omissions while comparing 10,492 clinical trials registered on both systems — 16.2 percent had differing completion statuses, and 33.9 percent of trials in both systems listed as “ongoing” on EUCTR were listed as “completed” on ClinicalTrials.gov. While it is unclear whether researchers, registry owners or both are responsible, the authors recommended that researchers request clarifications from the trialists, and that registries should cross-check data to ensure accuracy. The EBM DataLab recently launched its FDAAA Trials Tracker, which details U.S. studies that have not disclosed their results within one year of completion (CWWeekly, March 5). The full PLOS ONE see Industry Briefs on page 3.
Industry Briefs (continued from page 2)

article is available here: http://journals.plos.org/plosone/article?id=10.1371/journal.pone.0193088.

Novartis, Science 37 Expand Partnership for 10 Virtual Clinical Trials in Three Years

Novartis is expanding its alliance with Science 37 to initiate up to 10 new clinical trials over the next three years, blending virtual and traditional models while working toward a site-less model. The two companies previously initiated virtual trials for cluster headaches, acne and nonalcoholic steatohepatitis. Virtual trials use digital technology to allow certain trial aspects to be performed at home or a physician’s office, rather than a trial site. The new trials are expected to begin later this year in dermatology, neuroscience and oncology, with plans to allow patients to participate using mobile devices and telemedicine services.

Parexel Co-Founder Josef von Rickenbach to Step Down as CEO

Josef von Rickenbach, co-founder of Parexel, announced plans to step down as CEO last week, while continuing to serve as chairman of the board. The company appointed Jamie Macdonald to succeed him, effective March 15. Macdonald led INC Research, now known as Syneos Health, first as CEO and then as vice chairman, helping to take the company public in 2014. Before that, he served as the company’s chief operating officer. Macdonald has also served as senior vice president and head of global project Management at Quintiles, now known as IQVIA, and as chairman of the Association of Clinical Research Organizations board of directors in 2015. Von Rickenbach co-founded Parexel in 1982, and helped to expand the company to a valuation of over $5 billion dollars, with operations in over 100 countries.

Real-World Evidence (continued from page 1)

of the population, or following updates in electronic health records or other software, for example — reproducing the results can become much more streamlined.

Sponsors should incorporate an audit trail with version control, and set up firewalls between those doing analysis and researchers, the workshop recommended. Studies using more than one data source should report point estimates and confidence intervals individually, to illustrate variability in results.

Real-time monitoring should be segmented as well. “You don’t want to mix data streams. You want to see discontinuities,” Simon said. “You want to continuously monitor the quality of data streams so you see when something breaks.”

When it comes to validation, the industry needs to move away from comparing the results of a real-world study using observational treatment assignment to a randomized, controlled clinical trial, and showing they came up with the same result, Simon said.

“We’re deciding if the new method worked based on the answer it got — we need to have a way of deciding that upfront,” he added, citing the example used by former FDA Commissioner Robert Califf of drawing a bullseye around a hole in the side of barn, after the hole is already there.

In addition, new data-gathering and analysis tools should be validated not only against available tools, but against what’s happening in the real world.

“We have to do both,” said Califf, now vice chancellor for health data science at Duke University. “If we don’t ground it to the old tool, you can’t win the argument in the regulatory space or in the clinical review space, for example.”

“Sometimes our gold standard may not be so gold,” said Jesse Berlin, vice president and global head of epidemiology at Johnson & Johnson, who suggested the development of an open library of real-world data definitions and validated algorithms where all stakeholders could contribute. Common tools could bolster transparency, quality and efficiency in evidence generation.

“It should be illegal to write a custom piece of code to do a study,” said David Madigan, dean of the faculty of arts and sciences and professor of statistics at Columbia University. “It’s really crazy in this day and age. We should be using validated tools, not building things from scratch.”

“Building things from scratch is riddled with the potential for errors and is just intrinsically non-reproducible,” Madigan said, citing a published paper that said it “adjusted for age.”

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“Okay, so you try to reproduce that, and you go into the database and there’s somebody in there with an age of -3,” he said. “So what did they do with that? … The level of irreproducibility that we’re living with right now is unacceptable. The custom crafting of code is one of the root causes.”

However, as the field of pharmacoepidemiology has evolved in the past few years, tools such as the FDA’s Sentinel Initiative have grown with it, said Richard Platt, professor and chair of the department of population medicine at Harvard Pilgrim Health Care Institute.

Sentinel can now fully reproduce previous, large-scale, real-world data studies that relied on custom-built code, if only because nothing else was available at the time, he said.

“I think at the end of the day, it’s not only better, but substantially cheaper,” said Platt, who also serves as Sentinel’s principal investigator. “We’re now in a position where we can do better, clearly reproducible studies, using tools that can be as extensively vetted much faster and at a much lower cost than the old-fashioned way.”

To lower costs further, researchers and sponsors should decide where randomization and blinding are absolutely necessary, and examine the trade-offs when enrolling tens of thousands of patients, they said.

Randomizing treatment won’t lead researchers away from the right answer, “but the problem is it’s often crazy expensive, it takes a hugely long time, it’s a giant hassle, and patients and providers don’t like it — but besides that, what’s not to like?” said Simon.

While blinding of outcome assessments and analysis are important, blinding patients and providers may be less so, and at times unnecessary, he said. Requiring the treatment experience to be identical can obscure the truth of a product’s use in real-world settings.

And in such settings, sponsors should prepare to have study participants behave in unwanted ways — that is, as they would outside of a controlled trial environment.

As an example, a study examining the use of lithium to prevent repeated suicide attempts within the Veterans Affairs health system struggled with recruitment, with about 30 percent of potential patients being excluded for taking other medications.

The researchers argued to their institutional review board that these patients were necessary to mirror a real-world population, and they were allowed to be included with additional monitoring. In addition, unexpected events such as pregnancies should not be treated as protocol violations, but as something patients normally encounter in life.

These safety monitoring events can even be exploited as a benefit, said Michael Horberg, director of HIV and AIDS research at Kaiser Permanente.

In a major study of HIV pre-exposure prophylaxis treatment, or PrEP, patients were advised on safer sex and to use a condom, but the trial still resulted in over 120 pregnancies. However, they occurred without transmissions of HIV, helping to demonstrate the therapy’s effectiveness.

“When studying things that sometimes involve undesirable and stigmatized behaviors... unless we welcome in the way real world works, we’re never going to answer the question,” added Simon.

The academies’ third workshop, scheduled for July, will focus on approaches for operationalizing the collection and use of real-world evidence, including ways to supplement traditional clinical trials and challenges for incorporating its use into health systems and product development.
Another potential solution, Lamberti said, is pooling data from clinical sites to counter the siloing of data common among drug manufacturers. Sharing information with sites early on to assess study feasibility could enhance the site selection process, according to the Tufts report. Tufts researchers found that CROs are more efficient than drug sponsors, completing initiation an average of 5.6 weeks faster for repeat sites and 11 weeks faster for first-time sites. This was “very telling because there isn’t a lot of research out there comparing cycle times between sponsors and CROs,” Lamberti said. CROs make more use of advanced technology solutions for the study initiation process than drug sponsors, according to Tufts researchers, with 47 percent of CROs saying they used clinical trial management systems compared to only 28 percent of sponsors. More than half of sponsors still rely on spreadsheets, compared to just under one-third of CROs.

In addition, 10.9 percent of initiated sites are never activated — a constant figure over the past 20 years, according to Tufts — with sites being managed by CROs being activated more often.

More information can be found at http://csdd.tufts.edu/.

By Conor Hale

Pediatric antibacterial drug trials currently account for less than one percent of all interventional and observational pediatric studies registered on ClinicalTrials.gov between October 2007 and September 2015, or only 82 out of 12,703. According to a series of surveys conducted by the Clinical Trials Transformation Initiative, three of the four major barriers identified by respondents were related to parental involvement and consent.

They included obtaining consent when there is evident disagreement between two parents, parental concerns about the number of blood draws and invasive procedures required by the study protocol. Many parents are reluctant to give consent when they see no direct benefit for their child in a clinical trial and are happy with current care, one respondent said.

Interviews with parents found that each aspect of a study, from initial explanations to reporting the final result, can affect willingness to provide consent. Establishing trust and empathy, as well as providing clear transparency on any risks and benefits, were key decisionmaking factors, CTTI said, describing how parents’ priorities must be incorporated early into trial design for accrual to be successful.

All survey participants strongly preferred to hear about a clinical trial opportunity first from their child’s own pediatrician or from a doctor caring for them in the hospital — rather than being cold-called by a researcher or a stranger. In addition, being approached too soon or too often can be a detriment, such as during the first few days after birth, in the case of premature newborns in neonatal intensive care.

The remaining barrier related to overly narrow inclusion and exclusion recruitment criteria, including prerequisites disallowing the use of other antibacterial drugs prior to enrollment. Additionally, finding study coordinators with sufficient experience was a significant challenge, with one respondent recommending long-term staff support to help avoid constantly training new staff for each trial.

CTTI’s study identified several recommendations to help facilitate more studies. For example, pediatric trial networks can facilitate development and eliminate the need for startup with each new trial, as well as help standardize site resources and funding.

Another main factor was the ability to recruit study participants directly from the investigators’ own practice, the surveys found. Having dedicated staff available to enroll patients in inpatient studies with little advance warning, potentially 24 hours a day, was described as a major benefit.

Established referral systems, interdisciplinary collaborations and access to the hospital inpatient database were all listed as crucial for recruitment, and supporting the buy-in of other practitioners for their pediatric patients to enroll.
The study start-up phase sets the tone for a clinical research trial and is crucial to the overall success of a program. The critical nature of this phase places significant pressure on all stakeholders. The strength of the relationship between the site and CRO during study start-up is an important factor in creating a successful study outcome. Rather than a customer and vendor relationship, sites and CROs should strive to develop strategic alliances, partnering seamlessly through an entire clinical study and beyond. The study start-up stage offers ample opportunities for sites and CROs to establish the foundation of a trust-based relationship.

The feasibility and study start-up stage is a fundamental predictor of success and a key indicator of a site’s performance. CROs utilize this essential period as an opportunity to evaluate a site’s responsiveness and follow-up, and analyze the quality and accuracy of the information provided. All stakeholders are clearly invested in ensuring a highly productive, efficient clinical trial — therefore selecting high performing sites is critical to this success. When a few, high performing sites take on the majority of the work involved, CROs strive to implement processes to distribute the workload more evenly among all sites. Many CROs implement internal processes during feasibility aimed at distributing the workload more evenly among all sites. (See Figure 1.)

Sites should take advantage of the study start-up stage to conduct reciprocal feasibility on the CRO. How quickly does the CRO respond to requests for information? Will there be adequate training and patient recruitment support throughout a trial? If there are needs at the site level that may benefit from the additional resources a CRO can provide, they should be addressed as early as possible.

Clearly defining the roles and responsibilities as early as possible is extremely valuable to the overall relationship between a site and CRO. The beginning of a clinical study is a key time to establish the parameters of the study and outline expectations and responsibilities. Both parties can work together to set realistic goals and timelines that are mutually agreeable.

As clinical trials grow in complexity, it is increasingly common for sponsors to plan for earlier CRO involvement, often shifting CTA negotiations between sites and CROs. In addition to setting up the site budget for a specific trial, the two parties can work together to set up a master agreement for future studies. Ultimately, this will shorten the start-up timeline for additional projects, effectively making the CRO/site pair more attractive to a Sponsor.

CROs should consider providing a single point of contact to a site during a trial as roles and responsibilities are established. This is not always feasible; however, it is important for CROs to remain cognizant of the amount of pressure that sites are facing from working with multiple sponsors and CROs on other trials. CROs can help mitigate some of this pressure by ensuring that any contact is intentional and productive. Assigning a Site Relationship Manager or Site Liaison specifically to interact with sites is becoming more common.

A contract signature is merely the beginning of an open dialogue between a site and CRO. There are numerous opportunities throughout the feasibility and study start-up phase when both sides can work toward establishing a unified front. Ultimately, all entities involved in a clinical trial will benefit from a strong site and CRO partnership.

Brittany Parker is the Director of Marketing and Communications at Total Clinical Trial Management. She works closely with research sites and study staff to execute current programs and develop ongoing, long-term relationships. Please visit www.totalcro.com for more information.
# Drug & Device Pipeline News

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Bioverativ Announces First Patient Dosed in Study for Treatment of Cold Agglutinin Disease

Bioverativ announced that the first patient has been dosed in the Phase III clinical program of its investigational therapy BIVV009 for cold agglutinin disease (CAgD). The Phase III program includes two parallel Phase III trials, Cardinal and Cadenza, which are evaluating the efficacy and safety of BIVV009 in adult patients with primary CAgD, a disease with no approved therapies. The study assessed the long-term efficacy, safety and PK/PD profile of BIVV009 in six severely anemic primary CAgD patients. Primary and secondary outcome measures were achieved in the CAgD patients in the study. Hemoglobin levels increased in all six patients (median >4g/dl) which eliminated the need for transfusions while on treatment. There were no serious AEs assessed as related to BIVV009 by the investigator.

Dermira’s Two Phase III Trials for Acne Vulgaris Did Not Meet Co-Primary Endpoints

Dermira announced that the investigational treatment olumacostat glasaretil (formerly DRM01) did not meet the co-primary endpoints in its two Phase III pivotal trials (CLAREOS-1 and CLAREOS-2) in patients nine years of age and older with moderate-to-severe acne vulgaris. The Phase III clinical program included two randomized, multi-center, double-blind, parallel-group, vehicle-controlled trials, CLAREOS-1 and CLAREOS-2. The program assessed the efficacy and safety of olumacostat glasaretil compared to a potential New Drug Application (NDA) submission to the U.S. Food & Drug Administration (FDA). The program enrolled a total of 1,503 patients (CLAREOS-1, n=759 and CLAREOS-2, n=744) at 94 sites in the United States, Canada and Australia. In each trial, patients were randomized in a 2:1 fashion to receive either olumacostat glasaretil at a concentration of five percent or vehicle twice daily for 12 weeks. No treatment-related serious adverse events were reported, and no new or unexpected events were observed. None of these co-primary endpoint results were statistically significant.

Aimmune Therapeutics Presents Positive Results for Peanut Allergy Trial

Aimmune Therapeutics announced that the results of its pivotal Phase III PALISADE trial of AR101 for the treatment of peanut allergy. PALISADE studied the efficacy and safety of AR101 in peanut-allergic patients by assessing reductions in clinical reactivity to peanuts. PALISADE enrolled a total of 554 patients ages 4-49 with the primary analysis of patients ages 4–17. The trial met its primary and secondary endpoints, and AR101 demonstrated an encouraging tolerability and safety profile over the course of approximately one year of treatment. After treatment, patients completed an exit DBPCFC. The median tolerated dose of peanut protein in the entry DBPCFC was 10 mg, the equivalent of approximately 1/30 of a peanut, and, at baseline, 43 percent of patients had a peanut-specific IgE level >100 kU/L. There were no deaths or suspected, unexpected serious adverse reactions (SUSARs) in the trial, and the incidence of serious adverse events (SAEs) was low, as 1.1 percent of AR101 patients experienced SAEs that were possibly related to treatment. Most AR101 patients (85.5 percent) did not experience any investigator-reported systemic hypersensitivity reactions (SHRs) during the trial.

Esperion Announces Results of Bempedoic Acid Study

Esperion announced positive top-line results from the first pivotal, Phase III study (Study 4 or 1002-048) of bempedoic acid. The 12-week study met its primary endpoint with LDL-C lowering totaling 28 percent (p<0.001). The LDL-C lowering for the bempedoic acid group was 23 percent from baseline, as compared to an LDL-C increase of five percent for the placebo group. Patients treated with bempedoic acid also achieved a significantly greater reduction of 33 percent in high-sensitivity C-reactive protein (hsCRP), compared to the placebo group which had an increase of two percent (p<0.001). The 12-week, global, pivotal, Phase III randomized, double-blind, placebo-controlled, multicenter study evaluated the efficacy and safety of bempedoic acid 180 mg/day versus placebo as add-on therapy in patients with atherosclerotic cardiovascular disease (ASCVD), or at a high risk for ASCVD. The primary objective was to assess the 12-week LDL-C-lowering efficacy of bempedoic acid versus placebo when added to ezetimibe and up to the lowest starting dose of a statin.

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<td>The Clinical Trials Office at Reading Hospital has been specifically designed to meet the competitive demands of industry-sponsored trials. With investigators from diverse specialties, the clinical trials team serves as the fulcrum for excellent communication and service.</td>
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