Role of Real-World Evidence in Clinical Trials

By Brandon May and James Miessler

Using real-world data (RWD) and real-world evidence (RWE) in clinical trials is growing in popularity among both industry and the FDA, but both groups agree that all stakeholders need to be on the same page when it comes to definitions and ways to measure results.

“There is a tremendous interest in making use of the vast amount of data that’s already been collected in healthcare systems to more efficiently generate evidence,” the FDA’s Robert Temple told participants at a joint FDA and Duke University workshop last week.

“What people mean by RWE, and the specific study designs to be considered, is not clear,” said Temple, who is deputy director for clinical science in the agency’s Center for Drug Evaluation and Research. “In fact, the specifics of the data generated by an RCT (randomized clinical trial) within a healthcare system could vary tremendously.”

In a draft guidance issued in May, the FDA provides the following definitions:

- RWD are data relating to patient health status and/or the delivery of healthcare that are routinely collected from a variety of sources; and
- RWE is the clinical evidence regarding the usage and potential benefits or risks of a medical product derived from analysis of RWD.

But even these definitions may not entirely solve the problem, according to comments on the draft guidance the agency see Real-World Evidence on page 4.

Ask the Experts: Consent and Reconsent

This monthly feature presents a variety of questions from clinical trial professionals with answers from WCG Clinical’s expert staff. To ask a question of WCG’s experts, click here: https://bit.ly/2XB9F6R.

Question:

When a research activity includes a translated consent form, does the principal investigator need to sign both the translated consent form and the English consent form?

Answer:

The regulations for informed consent are divided into those that govern the contents of informed consent documents and those that describe the requirements for documenting consent (i.e., signing informed consent forms). There are no regulations that specifically address translations. In fact, the word “translation” does not appear in the regulations.

As a result, the requirements for signing translated consent forms are no different than they are for original forms. In an FDA-regulated clinical trial, both the participant and the person obtaining consent should sign and date the consent document that was used to facilitate the process with the participant. If a consent process was conducted in Korean using a Korean-language document, then that is the document that should be signed.

In addition to the standard approach to documenting informed consent, 21 CFR see Ask the Experts on page 5.
Up and Coming

This feature highlights changes in clinical research organizations' personnel.

Healthix
Healthix has announced that Todd Rogow will lead the organization as its new president and chief executive officer. Rogow previously served as senior vice president and chief information officer at the company.

TRANSEARCH
Larry Glines has joined TRANSEARCH International as managing director for life sciences and healthcare. Glines previously was president of Glines Associates, an executive search firm devoted to the healthcare and life sciences industry, a company he founded in 1995.

Carrick Therapeutics
Carrick Therapeutics has announced the appointment of Tim Pearson as chief executive officer. Pearson previously was executive vice president and chief financial officer for TESARO. Elaine Sullivan will step down as CEO and will continue with the company as executive entrepreneur and advisor to the board of directors, based in Dublin.

Veracyte
Keith Kennedy has been appointed chief operating officer, in conjunction with his current role as chief financial officer, effective immediately, at Veracyte. Prior to joining Veracyte as CFO in 2016, Kennedy served in key executive leadership positions at MCG Capital, Arlington Capital Partners and GE Capital.

Viela Bio
Viela Bio has named Mitchell Chan to the position of chief financial officer. Chan previously served as Viela’s vice president, head of finance and corporate strategy.

Squarex
Jack Talley has been appointed chief executive officer at Squarex. Talley currently serves on the board of Mitotherapeutix and recently served as CEO, president and director of Izun Pharmaceuticals.

Pharmaceutics International
Pharmaceutics International, Inc. (Pii) has announced the expansion of its commercial team. Wayne Ideus has been named senior director, business development; Wayne Grellner has been appointed senior director, business development; and Ryan McFarlane has been named executive director, business management. Ideus was previously key account director with Mallinckrodt Pharmaceuticals. Grellner was most recently director, global business development at Samsung. McFarlane was previously executive director of global marketing operations and global enrollment operations at Accelerated Enrollment Solutions.

Platelet BioGenesis
Sam Rasty has been named president and chief executive officer at Platelet BioGenesis. Rasty was most recently chief operating officer of Homology Medicines, Inc.

Smithers Avanza
Smithers Avanza has appointed Frank Rotella as director of operations. Rotella most recently served as manager of bioanalysis at Syneos Health.

HighTide Therapeutics
HighTide has named Adrian Di Bisceglie as chief medical officer. Di Bisceglie was previously professor of internal medicine and chief of hepatology, division of gastroenterology and hepatology at St. Louis University.

Amplity Health
Pravin Wilfrid has been named chief technology officer at Amplity Health. Wilfrid most recently held roles as CIO/SVP at HTA/Verra Mobility.

Inari Medical
Thomas Tu has been appointed chief medical officer and chief business officer at Inari Medical. Tu is the CEO and president of World Health Initiative and most recently was the director of the cardiac cath lab at Louisville Cardiology.

Royal Philips
Britta Lesaux has been named president and chief executive officer at Philips Canada. Lesaux was formerly the executive director of the health care business group at 3M Canada.

Teckro
Teckro has expanded their leadership team. Brendan Buckley has been appointed chief medical officer; Kelly Brown has been named chief marketing officer; Sandra Blaser has been made vice president of customer success; Anita Callan has been appointed vice president of engineering. Buckley served as chief medical officer and executive vice president of ICON from 2011-2017. Brown was previously vice president of marketing in Europe for Veeva Systems. Blaser established the customer success function for Veeva Systems in Europe. Callan most recently held product and content strategy positions at Aer Lingus. Flanagan was previously head of digital operations at Munich Re.
Presenting Live Procedures in Device Trials Raises Special Consent Issues

Clinical trials that ask participants to allow live broadcast or recording of their procedures must go to extra lengths to ensure proper informed consent, the FDA says.

In a final guidance aimed at clinical investigators and IRBs, the agency discusses special assurances that should be included in the informed consent procedure, including a statement that participating in a “live case presentation” provides no additional direct benefit to the patient. The subject also should be told that participation is optional.

The informed consent for a live case presentation may be a separate document, the agency says, as long as it clearly outlines any differences between the live procedure and the study protocol, and explains additional risks that may be presented by the live procedure, including to subject confidentiality.


FDA Guidance Sets Criteria for Trials of Hormonal Contraceptive Drugs

Trials of hormonal pregnancy prevention drugs would need to apply narrow enrollment criteria under a new FDA draft guidance released last week.

According to the guidance, trials should enroll nonpregnant, premenopausal women who have no history of infertility, engage in regular heterosexual vaginal intercourse with a normally fertile partner, have regular menstrual cycles and show no evidence of dysplasia or invasive cervical cancer upon screening. Trials also should represent all ages of premenopausal women, including adolescents.

In addition to enrollment criteria, the guidance advises on study type and length. Single-arm, open-label, historically controlled trials of at least one year in length are usually adequate for establishing efficacy, it says. Longer-lasting trials are recommended for long-acting reversible contraceptives like intrauterine systems. Shorter trials may suffice for products that include drug substances with well-characterized safety profiles.

Comments on the draft guidance are due by Sept. 11.


Altimmune to Acquire Spitfire Pharma

Altimmune has announced it will acquire Spitfire Pharma, including its product candidate SP-1373, a potent GLP-1/Glucagon receptor co-agonist for the treatment of NASH.

Spitfire, a portfolio company of Presidio Partners, was founded for the sole purpose of developing the NASH drug candidate, which will be renamed ALT-801. Altimmune hopes to begin phase 1 testing in 2020.

FDA Issues Recommendations on Pharmacokinetic Analysis in Trials

The FDA released a draft guidance on Thursday on the use of population pharmacokinetic analysis by sponsors of drug and biologic trials.

Population PK analyses can help in selecting dosing regimens, sampling schemes, exposure metrics and in pediatric study designs, the agency says. Population PK models can also be used to simulate drug exposures that are expected to occur following doses or dosing regimens that have not been directly investigated in prior clinical trials.

Comments on the draft guidance are due by Sept. 11.

Real-World Evidence

has received. While they applaud the FDA’s attempts to incorporate real-world evidence (RWE) into regulatory decisionmaking, two major sponsors’ comments indicate more work is needed.

Pharma giants Novartis and Gilead believe the agency’s draft guidance on identifying drug submissions that use RWE is too limited in scope — while the Association of Clinical Research Organizations (ACRO) recommended adding standardized summary assessments of the quality of data underlying RWD submissions. The association also recommended adding a glossary of key terms to aid understanding.

The clinical evidence listed for RWE in the guidance is too limited, Novartis said, suggesting the agency expand its scope to include patient reported outcomes (PROs) and quality-of-life factors.

Novartis stressed that the guidance needs to clearly distinguish between RWD and RWE and asked the agency to clarify how RWE can be applied in single-arm trials that lack external/historical arms.

Gilead also recommended that the guidance be expanded. The company said the agency should include sNDAs and sBLAs in its list of submissions and allow lab data linked to medical claims or electronic medical records as a source of RWD. Additionally, the different types of observational studies — cohort, case control and cross-sectional studies — should be detailed.

Speakers at the FDA workshop rang the same bell, saying the ability to accurately define and quantify outcomes that matter most to decisionmakers (e.g., patients, clinicians, regulators, payers and caregivers) has remained elusive.

“An exploding amount of RWD, paired with new and increasingly sophisticated methods of turning that RWD to RWE, have demanded a call to make that evidence actionable for a wide range of clinical decisionmakers.”

—Gregory Daniel, Margolis Center for Health Policy, Duke University

Accuracy, validity and reproducibility of RWD used to generate RWE are a cause of concern. Electronic health records, for instance, may be helpful for identifying outcomes of prescribing practices but lack insight on medications filled or dispensed.

And in the process of measuring outcomes in RWD, some form of measurement error will inevitably occur, said Sean Tunis, founder and director of Stanford University’s Center for Medical Technology Policy. The key is to measure and account for that error. “Ignoring measurement error and reporting about error but not correcting for it is bad practice,” Tunis said.

The discussion of RWE’s role in clinical trials also is taking prominence in the UK. The National Institute for Health and Care Excellence (NICE) has issued its own call for comments on plans for using real-world data.

NICE is considering using data from audits of procedures, registries that collect data on how particular treatments are used, surveys of patients using services, and data on national trends, such as the number of people who have a condition. The deadline for submitting comments to NICE is Sept. 13.

Read the nine comments on the FDA draft guidance here: https://bit.ly/2XHjTxF.

50.27(b)(2) also permits the use of a short-form consent document. Short-form consent documentation is typically used when an individual participant speaks a language for which there is no prepared translation. In this situation, the research site may utilize a short-form written consent document stating that the elements of informed consent have been presented orally to the participant or the participant’s legally authorized representative.

The short-form process also requires the presence of a witness to the oral presentation. When the short-form approach is used, there are additional documentation requirements. In these situations, the short form is signed by the participant (or the representative) and the witness. In addition, the witness also signs the English-language consent document along with the person obtaining the consent. A copy of both the English-language consent document and the short form must be given to the participant. Many IRBs have short-form templates in several foreign languages.

In addition to consent process considerations, the enrollment of non-English speaking participants should be approved by the sponsor and consideration should be given to the impact of the language barrier on data collection. For example, participant diaries and other instruments may only be available in English. When there is an update to informed consent information, the first question to consider is which of the study participants may need to know this information. If the change is related to screening procedures, then participants who are already on the study drug won’t reconsider study participation because of that change. A revision to the drug dosing schedule won’t matter to participants who have completed dosing and are in the follow-up phase. New information that secondary cancers may be seen in people who receive this class of drug, even years later, would be important to future, current and past participants; if they’ve finished dosing, it can’t affect their decision about being in the study, but it may impact their future clinical care.

In this case, if participants are just waiting for a final follow-up call, do the changes to the consent information impact their participation or their future clinical care? If not, it may be reasonable to say that they don’t need to be reconsented at all. But if it does impact them, then the next question is the process.

FDA regulations allow a waiver of documentation of informed consent, which means that the consent process can be conducted verbally and a note can be written to document that the participant provided consent, without having their actual signature (56 CFR 109.1). The FDA also announced in late 2018 that it will allow a waiver of informed consent in certain circumstances.

In your example, if it is appropriate to inform the participants in follow-up, it may be that obtaining verbal consent with documentation of that agreement in their research record is sufficient and it is not necessary for the informed consent document to be mailed and returned. It may even be better to rely on verbal consent, as some organizations are uncomfortable with obtaining signatures remotely, as there is no way to tell who actually wrote the signature when it is unwitnessed.

Usually, the reviewing IRB will include directions for who needs to be reconsented when they approve the revised consent information, but not all IRBs do this. The sponsor can certainly suggest a plan for who should be reconsented and how reconsent will be obtained (e.g., signing the new written consent form for new participants and those on the study drug, and waiver of documentation of consent requested to allow verbal reconsent by phone for participants off study drug but in long term phone follow-up), which may be logistically feasible and less burdensome on both staff and participants.
Setting you Up for Success from the Start.

At WCG, we use our evidence-based insights to help set you up for success from the start. From strategic site selection to accelerating enrollment, our solutions empower you to anticipate problems, make better decisions and gain greater control over the key elements of your clinical study startup.

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## Drug & Device Pipeline News

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<tr>
<th>Company</th>
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<th>Status</th>
<th>Sponsor Contact</th>
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<tr>
<td>Emmaus Life Sciences, Inc.</td>
<td>pharmaceutical-grade L-glutamine (PGLG)</td>
<td>diverticulosis</td>
<td>Phase 1 trial initiated enrolling 10 patients at multiple sites</td>
<td>emmauslifesciences.com</td>
</tr>
<tr>
<td>Enanta Pharmaceuticals, Inc.</td>
<td>EDP-514</td>
<td>hepatitis B virus (HBV)</td>
<td>Phase 1a/1b trial initiated enrolling 98 subjects</td>
<td>enanta.com</td>
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<tr>
<td>Neurovive Pharmaceutical AB</td>
<td>KL1333</td>
<td>mitochondrial disease</td>
<td>Phase 1a/1b trial initiated enrolling healthy subjects in the UK after successful completion of the first stage of enrollment</td>
<td>neurovive.com</td>
</tr>
<tr>
<td>Auris Medical Holding Ltd.</td>
<td>AM-201</td>
<td>antipsychotic-induced weight gain and somnolence</td>
<td>Phase 1b trial initiated enrolling healthy volunteer subjects in Europe</td>
<td>aurismedical.com</td>
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<tr>
<td>4D pharma plc</td>
<td>MRx-4DP0004</td>
<td>asthma</td>
<td>Phase 1/2 trial initiated enrolling 90 subjects not adequately controlled on their current inhaler maintenance therapy</td>
<td>4dpharmaplc.com</td>
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<tr>
<td>Vedanta Biosciences</td>
<td>VE416</td>
<td>peanut allergy</td>
<td>Phase 1b/2 trial initiated enrolling 40 subjects 12 years of age and older at MassGeneral Hospital for Children in Boston</td>
<td>vedantabio.com</td>
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<tr>
<td>ActoBio Therapeutics, Inc.</td>
<td>AG019</td>
<td>early-onset type 1 diabetes (T1D)</td>
<td>Phase 1b/2a trial initiated enrolling subjects 12 to 17 years of age</td>
<td>actobio.com</td>
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<tr>
<td>ActoBio Therapeutics, Inc.</td>
<td>AG019 combined with teplizumab (PRV-031)</td>
<td>early-onset type 1 diabetes (T1D)</td>
<td>Phase 1b/2a trial initiated enrolling adult subjects</td>
<td>actobio.com</td>
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<tr>
<td>Biohaven Pharmaceutical Holding Company Ltd.</td>
<td>rimegepant</td>
<td>treatment refractory trigeminal neuralgia</td>
<td>Phase 2 trial initiated enrolling subjects at Johns Hopkins Medical Center</td>
<td>biohavenpharma.com</td>
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<tr>
<td>GlaxoSmithKline</td>
<td>otilimab</td>
<td>moderate to severe rheumatoid arthritis (RA)</td>
<td>Phase 3 trial initiated</td>
<td>gsk.com</td>
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<tr>
<td>BiondVax Pharmaceuticals Ltd.</td>
<td>M-001</td>
<td>influenza</td>
<td>Phase 3 trial initiated</td>
<td>biondvax.com</td>
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<tr>
<td>Alexion Pharmaceuticals, Inc.</td>
<td>SOLIRIS (eculizumab)</td>
<td>neuromyelitis optica spectrum disorder (NMOSD) in adult subjects who are anti-aquaporin-4 (AQP4) antibody positive</td>
<td>Approval granted by the FDA</td>
<td>alexion.com</td>
</tr>
<tr>
<td>Janssen</td>
<td>DARZALEX (daratumumab) in combination with lenalidomide and dexamethasone (Rd)</td>
<td>subjects with newly diagnosed multiple myeloma who are ineligible for autologous stem cell transplant (ASCT)</td>
<td>Approval granted by the FDA</td>
<td>janssen.com</td>
</tr>
<tr>
<td>Pfizer</td>
<td>ZIRABEV (bevacizumab-bvzr)</td>
<td>metastatic colorectal cancer; unreseetable, locally advanced, recurrent or metastatic non-squamous non-small cell lung cancer (NSCLC); recurrent glioblastoma; metastatic renal cell carcinoma (RCC); and persistent, recurrent or metastatic cervical cancer</td>
<td>Approval granted by the FDA</td>
<td>pfizer.com</td>
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For news on trial results, FDA approvals and drugs in development, Join the LinkedIn Drug Research Updates group!
# Drug & Device Pipeline News

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<tr>
<td>Janssen</td>
<td>Darzalex (daratumumab) in combination with lenalidomide and dexamethasone as a first-line treatment</td>
<td>multiple myeloma subjects who are ineligible for autologous stem cell transplant (ASCT)</td>
<td>Approval granted by the FDA</td>
<td>janssen.com</td>
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<td>Genmab</td>
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<td>genmab.com</td>
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<tr>
<td>Alexion Pharmaceuticals</td>
<td>Soliris (eculizumab)</td>
<td>neuromyelitis optica spectrum disorder (NMOSD) in adult subjects that express a specific biomarker</td>
<td>Approval granted by the FDA</td>
<td>alexion.com</td>
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<td>Teva Pharmaceuticals</td>
<td>1% Sodium Hyaluronate</td>
<td>osteoarthritis (OA) of the knee in subjects who have failed to respond adequately to conservative non-pharmacologic therapy and simple analgesics (e.g., acetaminophen)</td>
<td>Approval granted by the FDA</td>
<td>tevapharm.com</td>
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<td>Retrophin</td>
<td>Thiola EC (tiopronin) 100 mg and 300 mg tablets</td>
<td>cystinuria</td>
<td>Approval granted by the FDA</td>
<td>retrophin.com</td>
</tr>
<tr>
<td>Grifols</td>
<td>Xembify 20% subcutaneous immunoglobulin</td>
<td>primary immunodeficiencies</td>
<td>Approval granted by the FDA</td>
<td>grifols.com</td>
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Upcoming Event Highlights

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<td>SEPTEMBER 4-5, 2019</td>
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<td>Clinical Trial Risk &amp; Performance Management Summit</td>
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<td>Philadelphia, PA</td>
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<td>SEPTEMBER 27-29, 2019</td>
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<td>Society of Clinical Research Associates 2019 Annual Conference</td>
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<td>San Antonio, TX</td>
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<td>OCTOBER 23-25, 2019</td>
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<td>FDA Inspections Summit</td>
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<td>Bethesda, MD</td>
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<td>OCTOBER 27-30, 2019</td>
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<td>MAGI Clinical Research Conference 2019 West</td>
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<td>Las Vegas, NV</td>
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Webinar

AUGUST 15, 2019

Real World Evidence and Data: A Tufts Study of 30 Pharma Companies
1:30 p.m. – 3:00 p.m. EDT

Based on their knowledge, and using several recent case studies, Dr. Mary Jo Lamberti — associate director of sponsored research at the CSD — and Francis Kendall — senior director at Cytel — will share valuable information on:

- Types of technology used to access or collect RWD and evidence and partnerships that support usage
- Significant challenges to using RWD as well as strategies and practices that impact return on investment or performance
- The key drivers for change and the adoption of RWE
- And more