Pediatric Clinical Trials: Special Challenges, Hidden Costs
By Mike Ingram

As difficult as the informed consent process can be in adult trials, involving children in studies adds unique and complex challenges, says one pediatric research expert.

Navigating the rules for parental permission and participant assent in pediatric clinical trials can be tricky, said Lisa Benson, senior vice president for research, education and quality at the Institute for Advanced Clinical Trials for Children, speaking at a recent CenterWatch webinar. Ethical and regulatory considerations can change based on the specific risks of a given study and the age of the study participants, Benson said.

To understand the permission/assent rules, study sponsors and sites first need to understand the additional protections laid out by federal regulation for children participating in clinical trials, she emphasized. Those regulations break studies into four potential categories:

- Minimal risk;
- Greater than minimal risk, but with the potential for direct benefit to the participant; and
- Greater than minimal risk, with no direct participant benefit, but likely to yield generalizable knowledge.

A fourth category exists for studies that do not fall under one of the other three and are not otherwise approvable but nevertheless present an opportunity to address a serious health problem in children. In this category, studies must be approved by a special committee convened by the FDA.

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EU’s Privacy Rule Impacts Sites, Sponsors Globally
By Gienna Shaw

“IT’s a little bit challenging to look at activities and data processing and to figure out ‘does this apply to me?’” said attorney Melissa Markey of Hall, Render, Killian, Heath & Lyman at a recent MAGI-sponsored webinar.

The first step is to determine whether your sponsor, CRO or trial site meets one of three criteria:

- Established in the EEA and acting as a data controller or processor;
- Not established in the EEA but offers goods or services to data subjects located in the EEA; or
- Not established in the EEA but monitors the behavior of data subjects located in the EEA.

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**Gottlieb Announces Return to Private Sector Policy Development**

On his last day as FDA commissioner, Scott Gottlieb announced he will return to the American Enterprise Institute to work on drug pricing in a part-time capacity.

Gottlieb, who last month announced he was resigning from the FDA to spend more time with his family, will put in six days a month as a resident fellow at the D.C.-based conservative think tank. It’s a familiar role for Gottlieb, who began serving as a resident fellow at AEI in 2002 before being appointed as the FDA’s commissioner in May 2017.

National Cancer Institute director Ned Sharpless will now serve as the acting commissioner of the FDA until the White House nominates a new candidate. No plans for a new nomination have been announced.

**WCG Acquires Pain Med Developer Analgesic Solutions**

The WIRB-Copernicus Group last week announced its acquisition of Analgesic Solutions, a pain medication developer and supporter of clinical trials for pain-induced conditions.

The company advises research sponsors on protocol design and development, regulatory and FDA submissions, and signal-to-noise optimization.

Its Misuse, Abuse and Diversion Drug Event Reporting System (MADERS) is the first standardized system for classifying and quantifying abuse-related events in clinical trials. With applications that extend beyond the field of pain management, MADERS can be used in the trial of any drug that crosses the blood-brain barrier and therefore holds the potential for addiction.

**CRO Giant Joins ACRP’s Workforce Development Project**

Covance, one of the world’s largest CROs, has joined the Association of Clinical Research Professionals’ “Partners in Workforce Advancement” project, which aims to recruit the next generation of clinical trials leaders.

The CRO, which claims annual revenues above $2.5 billion, employs some 12,500 employees in 60 countries.

**Cancer Research Investor Announces CAR T-Cell Trials for Solid Tumors**

Stand Up to Cancer (SU2C) last week announced that it is funding two CAR T-cell therapy clinical trials it hopes will make headway in treating solid tumors.

CAR T-cell therapy has encountered multiple obstacles in dealing with solid tumors, such as identifying antigens to be targeted by the CAR T-cells, moving cells to tumors and keeping them there to attack cancerous cells, and dealing with the tumors’ immunosuppressive affects.

The collaboration between SU2C and the American Association of Cancer Research includes a Phase I clinical trial of regionally delivered CAR T-cells in treatment for malignant pleural disease, as well as a trial for the administration of HER2-CAR T-cells in patients with advanced sarcomas.

SU2C has invested more than $175 million in immuno-oncology research in the past 10 years.

**Novartis’ Acquisition Will Add Anti-Inflammatory Programs to Arsenal**

Novartis has reached a deal to acquire anti-inflammatory drug developer IFM Tre, an arrangement that will see one clinical and two preclinical anti-inflammatory programs added to the drug titan’s portfolio.

The two drugmakers reached a definitive agreement that includes an up-front $310 million payment from Novartis, in addition to a potential $1.265 billion in milestone payments.

The compounds Novartis is set to acquire include IFM-2427, a clinical-stage systemic antagonist for various chronic inflammatory disorders, such as atherosclerosis and NASH; a pre-clinical gut-directed molecule for treating inflammatory bowel disease; and a pre-clinical-stage CNS-penetrant molecule.

**Ironwood Completes Cyclerion Spin-Off**

Ironwood Pharmaceuticals has completed its $175 million spin-off of Cyclerion Therapeutics, which leaves the new entity with a portfolio of five orphan drugs and allows Ironwood to focus on gastrointestinal diseases.

Ironwood holds the rights to Linzess (linclotide) for irritable bowel syndrome, which the company expects to bring in revenue of up to $390 million. Ironwood has two candidate drugs in development, one to treat persistent gastroesophageal reflux disease and the other to treat abdominal pain associated with irritable bowel syndrome.

**BriaCell and Incyte Link Up for Breast Cancer Combo Therapy Collaboration**

Clinical-stage biotech company BriaCell and global biopharmaceutical company Incyte have joined forces in a clinical trial collaboration in which they will work to select novel...
combinations for treating breast cancer.

The non-exclusive collaboration agreement focuses on the selection of novel combinations for treating advanced breast cancer, but also will involve a Phase I/IIa clinical trial of BriaCell’s Bria-IMT, a cell line that prods a patient’s immune system into treating tumor cells as foreign. The trial will use novel compounds selected by Incyte.

BriaCell is also developing Bria-OTS, a personalized immunotherapy for advanced breast cancer.

**Chinese Regulators Approve Trials for Luye’s Eylea**

Biosimilar Chinese regulators have approved Luye Pharma’s request to open clinical trials for its new antibody drug, the Shanghai-based company announced last week.

Luye’s LY09004 is a biosimilar to Regeneron’s blockbuster Eylea (aflibercept) injectable, indicated for a variety of eye problems, including age-related macular degeneration and diabetic retinopathy.

Eylea has been a top earner for Regeneron. The company reported $1.08 billion in sales in the fourth quarter of 2018, an increase of 11 percent over the previous year.

The approval comes less than three months after Luye announced an agreement with AstraZeneca to market lipid-busting Xeuzhikang capsules in China, the first time a global pharma company had been granted exclusive authorization to market a drug that had been developed by an independent Chinese company.
Pediatric Clinical Trials
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HHS regulations define "minimal risk" as risk that's no greater than what a person may encounter in daily life, Benson said. "That may be a small blood sample, urinalysis, EEG, minor dietary changes, non-invasive swabbing and some standard psychological testing," she said. For studies in this category, an IRB often will determine that the consent of only one parent or guardian is sufficient for a child's participation.

For studies in the second category — where the risk is higher, but where there may be direct medical benefits to the study participant — an IRB must determine, on a case-by-case basis, whether one-parent consent is enough. But for studies falling into the third category, both parents will need to consent, unless one parent is deceased, unknown, incompetent or not reasonably available — which would need to be carefully documented, Benson said.

Depending on age and developmental stage, the child's assent may be required in addition to parental consent. The specific age range for child assent is sometimes governed by state law, Benson said, and many institutions as a rule of thumb use either 7-17 years or 10-17 years. For studies with clinical sites in multiple states, researchers need to track the rules for each state, in consultation with the IRB.

But how to obtain child assent? There's no single hard-and-fast method, Benson said. “Parents give the researcher permission to approach the child about participating in the research. So then it’s often a conversation between parent and researcher, or research staff, about what’s the best way to go about obtaining assent.” She added that it’s crucial to carefully document child assent.

IRBs can grant participant assent waivers in special circumstances. If the capability of the child is such that assent can’t be reasonably given, Benson said, or if the study offers the potential for direct benefit to the child that is available only in the context of the clinical investigation — as in certain oncology or hematology studies — a waiver may be granted. Waivers also may be granted for cases in which the research involves no more than minimal risk to the participant, if the research couldn’t be carried out without a waiver, and if the waiver won’t adversely affect the rights and welfare of the subject, Benson said.

The pediatric consent/assent process also can add costs because more documents are involved, and it’s important that a study budget take these complications into account, Benson said. Other hidden costs in pediatric studies include the need for additional amendments, study delays related to recruitment and retention, and longer visits.

“Something like a blood draw, just to put an IV in, most of the time [with a child] we’ll need EMLA cream, or some sort of sedative measure,” Benson says. “And what about procedures like x-rays or MRIs? Sedation may be needed, since children can’t necessarily lie still for 40 minutes.”

Social workers often will be required, to work with children, as well as child-life specialists who can provide play therapy during longer visits and distraction techniques tailored toward a pediatric population. Pediatric studies also can require travel budgets, since the subject populations tend to be smaller, requiring trials to expand their enrollment geographically. And since most children and youths can’t transport themselves to trial sites, entire families often travel to participate. This is especially true for rare-disease studies that can necessitate long family separations.

Too often, Benson said, study sponsors and sites don’t take these special pediatric considerations into account when budgeting for a clinical trial. “A lot of times, an adult trial has just finished, and now they want to put it into the pediatric population. And so they try to take the adult trial and fit it into a pediatric protocol.” But sites need to advocate for the additional funds they’ll need to carry out a pediatric study, especially to deal with protocol amendments. “We tend to see a lot of amendments [in pediatric studies], for instance, and we need to be compensated for the time and effort to put them together and have them reviewed.”

To listen to the webinar, go to: https://bit.ly/2uM6GYY.

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### EU’s Privacy Rule

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If a U.S.-based university has a campus or a pharmaceutical company has an affiliate in the EEA, for example, the rule applies regardless of whether or not the data processing takes place there.

Subjects’ citizenship doesn’t matter, either. If a subject is physically located in the EEA, that subject’s personal data falls under GDPR. On the other hand, collecting data from EU residents while they’re in the U.S. circumvents the GDPR, unless the organization has ties to or affiliates in the EU.

And determining what constitutes personal data under GDPR can be even trickier, Markey said.

Under the rule, personal data is defined as “any information relating to an identified or identifiable natural person … who can be identified directly or indirectly.” That goes beyond identifiers such as names to include identification numbers, location data and factors such as physical, physiological, genetic, mental, economic, cultural or social identity. Even trade union membership is considered personal data, under GDPR.

“If you think through that list, that’s an incredibly broad list of people,” said Markey. “As a result, it’s really hard to have any information about a person and not have it be identifiable data,” Markey said.

Of course, medical research would come to a grinding halt if researchers couldn’t use personal health data. So there are exceptions, said David Peloquin of Ropes & Gray LLC, but there must be a legal basis to support the processing.

One legal basis stands out — when the data subject has given consent. But while that seems easy to defend, in fact it’s not as simple as it sounds. GDPR doesn’t favor that option. Subjects may have a disease or condition and hope an experimental drug will help them, for example. In that case, consent is often considered not freely given, Peloquin said.

There are many other administrative obligations under GDPR. For example, the regulations call for research entities to appoint a data protection officer under some circumstances, such as when core activities require regular and systematic monitoring of data subjects on a large scale or core activities consist of processing on a large scale of special categories of personal data, which is often the case in clinical research.

Organizations also may be required to appoint a representative in the EEA to serve as a legal representative for clinical trials. Organizations must report data breaches, of course, within 72 hours of learning of the breach. Finally, controllers and processors must conduct a data protection impact assessment when the processing uses new technology or is likely to result in a “high risk to the rights and freedoms of subjects,” Peloquin said.

Creating a centralized process to coordinate all GDPR compliance factors is critical, according to Cerdi Beltre, senior vice president of institutional services for WIRB-Copernicus Group. The process should focus on three main areas: 1) the location of operations, 2) the role of the university/researchers and 3) the location of research subjects.

“Whether it is tied to the institutional approval process or an appendage of the ethical review process may not matter provided that, as an entity, you are aware of when you must adhere to the obligations under GDPR.” Markey and Peloquin will speak on GDPR and other data privacy regulations at the MAGI 2019 East conference in May: https://bit.ly/2AYxqbC.

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