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ePRO in Action for Phase II

By Shelia Rocchio

Sanofi Pasteur collects quality of life and safety data with eDiaries.

The global community is rallying to stop the increase of *Clostridium difficile*, a bacteria that spreads throughout the intestinal system causing diarrhea, fever, nausea, pain, and/or serious conditions such as colitis, which can result in death.

C. difficile is an anaerobic spore-forming bacterium, present asymptotically in approximately 60% of infants but only about 3% of healthy adults. It belongs to the Clostridium family of bacteria, which also includes *C. tetani* (tetanus) and *C. botulinum* (botulism). When the natural microbial flora of the gut is disturbed, usually as a result of antibiotics, and a patient ingests *C. difficile* spores, the bacteria can multiply and release the two toxins, which cause gastrointestinal pathologies in humans known collectively as CDI.

It is easy to contract *C. difficile*, and several studies show that it is a growing cause of illness especially in hospital patients. *C. difficile* is now among the most common causes of hospital-acquired infection in Europe and North America. In an effort to prevent the bacteria's propagation in the UK, the National Health Service has instituted a mandatory *C. difficile* reporting program. Last year, more than 35,000 cases of *C. difficile* were detected in British NHS hospitals and the bacteria were noted on the death certificates of 438 nursing home residents.

To add urgency to the need for a vaccine, researchers have identified a more virulent, antibiotic-resistant strain that spreads easily and causes greater morbidity and mortality.

Treatment of *C. difficile* infection includes the use of one of two antibiotics. Nonantibiotic approaches for managing *C. difficile* infection are badly needed, since the alteration of the gut flora associated with antibiotics triggers the infection in the first place. There is also considerable concern about the emergence of antibiotic-resistance in *C. difficile* and other bacteria. Vaccination has the potential to be a very effective strategy to combat gastrointestinal pathologies caused by *C. difficile*, along with improved antibiotic stewardship and infection control practices.

Developing vaccines

Sanofi Pasteur, the vaccines division of the sanofi-aventis Group, has a long history of developing vaccines to address significant, unmet medical needs and substantially improve current care standards. Sanofi Pasteur provided more than 1.6 billion doses of vaccine in 2008, making it possible to immunize more than 500 million people across the globe.

A Phase II clinical study of Sanofi Pasteur's *C. difficile* vaccine is currently ongoing in the UK and will soon expand to the United States. While the target indication for the vaccine is primary prevention of CDI, this trial in infected patients aims at providing proof of concept of the vaccine approach in patients with existing CDI, who are at risk for recurrent CDI disease symptoms.

Vicki Tyler, Clinical Trial Manager at Sanofi Pasteur's Massachusetts facility, oversees the study. She explained, "We have been conducting *C. difficile* research for quite some time. There is a huge unmet medical need

throughout the developed world. While new therapeutic agents are being developed by others to treat identified cases, the field has begun to recognize that prevention is the preferred strategy and there is no better approach to prevention than vaccination."

The Phase IIb trial involves more than 600 participants with acute CDI at about 30 centers in the UK and 45 in the United States, and began in the fall of 2009. Participants will be randomized to four study groups. Three groups will receive the vaccine, while the fourth will be given a placebo. All subjects will receive standard of care antibiotics.

Sanofi Pasteur's candidate vaccine uses a toxoid-based approach, which has been used extensively in the licensed vaccines against tetanus, diphtheria, and pertussis (whooping cough). This candidate vaccine has successfully completed Phase I clinical trials in more than 200 participants to evaluate its safety and immunogenicity.

ePRO implementation

Sanofi Pasteur had used electronic patient reported outcome (ePRO) solutions provider PHT Corporation in previous trials. "eDiaries motivate subjects to complete their daily questionnaires. In addition, it is much more efficacious to ask subjects how they feel at a precise moment and get an immediate, accurate answer," said Tyler.

PHT's eDiary, the LogPad, associates a time and date with every entry, ensuring researchers know exactly when subjects completed their reports. With paper diaries, researchers can only assume people remember to actually record time while completing the diary and that the information is accurate.

Moving to ePRO in Phase II was also advantageous because Sanofi Pasteur wanted to conduct long-term follow up and hoped the eDiaries would, in addition to fostering a solid relationship between investigators and subjects, be helpful further along when they became patients again. "Sites have a daily electronic connection with subjects," Tyler said. "Because the LogPad gives subjects an important connection to the study, we are more likely to keep them engaged all the way to the end of the trial and beyond."

For Phase I, Sanofi Pasteur tested healthy volunteers rather than subjects with *C. difficile*. These initial studies evaluated various dose levels to determine how volunteers would respond. The Phase II trial seeks to evaluate various dose levels in infected patients. In designing the Phase II trial, Sanofi Pasteur started with the Phase I questionnaire in order to analyze the data from both the Phase I and Phase II studies in combination. Sanofi Pasteur also included standard quality-of-life questions in the Phase II study, which are included on the LogPad.

The company's years of experience developing questionnaires related to vaccine studies allowed Sanofi Pasteur to work with PHT to create an easy, yet comprehensive, set of questions for the eDiary. Because Sanofi Pasteur was focusing on the elderly population in this study, they designed a thorough questionnaire with simple, multiple-choice questions to reduce burden. As a specific adaptation for this population, PHT provides a larger stylus.

Sanofi Pasteur collects a baseline before each subject receives the initial vaccination in the hospital. During the baseline period, subjects receive training on how to use the LogPad and use it daily to become accustomed to the device. On the evening of each injection day—at zero, seven, and 28 days—subjects complete a questionnaire that asks about nausea, stool, and bowel movements, as well as questions about the injection site and basic questions about their well-being. Then the subjects answer daily diary questions at home for seven days after the injection.

To ensure that all entries are confidential and secure, study participants sign their LogPads with a private access code. Questions appear on the screen according to how they respond to each previous question. If a subject

responds that he or she has abdominal pain, a follow-up question about abdominal pain comes up on the LogPad.

In training, subjects are asked to answer every question; the lack of a response automatically triggers an alert to their site to follow-up with the subject. Additionally, if subjects do not record data in their LogPads, sites may contact them to ensure they are not experiencing any issues with the LogPad or the trial. Site personnel along with CRO and Sanofi Pasteur project team members have secure, real-time access to real-time patient compliance data throughout the study via PHT's online data viewing portal, StudyWorks.

Electronic gains

Tyler said there are several significant benefits of using an eDiary over paper, for both sponsors and subjects. When a trial uses paper diaries, investigators expect that subjects will end up entering information when they're sitting in their cars before their scheduled visit. Now, investigators know they are receiving real-time information and that diary data is recorded at the times specified by the protocol. As an added trigger, the LogPads have an alarm feature that investigators set to remind subjects to complete their questionnaire every day.

To select the most appropriate eDiary system, Sanofi Pasteur vetted four vendors for this study. They cited the size of the screen, ease of use, and professional support as key factors in their decision to choose PHT LogPad.

Sanofi Pasteur expects to achieve specific improvements in the data gathering processes, data quality, patient compliance, and trial process efficiency by using eDiaries for Phase II. "Phase II study subjects are more conscientious about completing questionnaires," Tyler commented. "They enjoy using the electronic device and were delighted to learn how easy the LogPads are to use."

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