Too Many Amendments, Too Little Planning, Expert Says

By Gienna Shaw

The rise in the number of protocol amendments occurring before the first patient has even received the first dose is a reflection of failure in planning trial design, says Ken Getz, director of sponsored research programs at the Tufts Center for the Study of Drug Development.

Amending a protocol often means adding endpoints, distinct procedures and patient visits that may not be strictly necessary, Getz said in a webinar last week. “You don’t have to gather data or report on every finding,” he said.

Sometimes added complexity comes from risk avoidance: Companies want to hedge against even a slight chance that a regulatory agency will ask a question. It is also borne from the trend of gathering subjective outcomes and comparative effectiveness data or incorporating additional data from sources such as wearables and smartphone apps.

“No one is questioning the strategic value of many of these supporting tertiary and exploratory endpoints,” Getz said. “The

Clinical Trials Are About Hope and Possibilities, Author and Trial Veteran Says

In 2011, Mary Elizabeth Williams was diagnosed with metastatic melanoma, a finding that usually means a patient has six to seven months to live. Knowing melanoma doesn’t respond well to traditional cancer treatments, she decided to take a chance on a phase I immunotherapy trial of a new drug. Williams wrote about her experience in her book, A Series of Catastrophes and Miracles: A True Story of Love, Science and Cancer. It was a journey, she says, from last resort to hope and possibilities.

Lindsay McNair, chief medical officer of WCG, spoke with Williams in a webinar last week, discussing the patient perspective on clinical trials, what they do right and how to change what they do wrong.

Q Given your options — treatment that didn’t offer a good success rate, death or participating in a clinical trial — do you feel that you were well informed on your options and what participation in a clinical trial entailed?

At the time, Yervoy (ipilimumab) was a very new drug on the market and had a 30 percent success rate. It’s scary embarking on a course of treatment for which there is very little precedent. There were not a lot of human subjects who had come before me, and I knew that the risks could be great. There was a risk, not only of it not working, see Clinical Trials on page 5

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WCG Welcomes Applicants for New Global Research Network

WIRB-Copernicus Group (WCG) is inviting clinical researchers to apply for membership in its Global Research Network (GRN), a free service that offers networking opportunities, trial insights and sponsor connections.

Members of the network will have access to WCG’s broad collection of clinical trial metrics and analytical data to help them compare their sites’ performance to the rest of the industry. GRN also allows members to participate in WCG webinars, thought leadership events and roundtable discussions.

The network also supplies sponsors and CROs with information on its members’ capabilities and clinical research interests, giving members access to more industry-sponsored trials. “We aim to make sites more attractive and effective in study conduct,” says Jonathan Zung, WCG executive vice president.

WCG also recently announced its SiteReady suite, an end-to-end solution to help institutions and independent sites improve research efficiency and profitability.


FDA Issues Guidelines on Pediatric HIV Treatments, Prevention

The FDA last week issued two final guidance documents that the agency hopes will help drug sponsors develop more effective HIV prevention medicines and HIV treatments for children.

The agency urges drug sponsors to include adolescents — defined as children between 12 and 17 years old — in Phase III adult trials. Sponsors should begin pediatric formulas as soon as Phase II trials have helped to zero in on the adult dose.

In a separate guidance on HIV prevention, the FDA recommends that trial sponsors include healthy, infection-free adults who are “at substantial risk” of becoming infected.

Generally, the agency looks for “two adequate and well-controlled trials” to demonstrate a treatment’s effectiveness. But a single Phase III trial might prove useful “if the results are robust with internal consistency, clinical and statistically persuasive and supported by additional evidence.”

Read the pediatric HIV infection guidance here: https://bit.ly/2TY3gQr.


Natural Histories Can Help in Designing Rare Disease Trials, FDA Says

A new FDA draft guidance encourages sponsors of rare disease trials to use natural history studies — observational studies that track the course of a disease — when developing rare disease trials.

The agency has promised to make more room for such real-world evidence studies in the hopes of speeding up drug development for rare diseases.

According to the draft guidance released last week, natural histories can help zero in on patient populations, figure out ways to measure clinical outcomes, identify or develop biomarkers and even design externally controlled studies.

“Information obtained from a natural history study can play an important role at every stage of drug development,” said FDA Commissioner Scott Gottlieb in a statement, “from drug discovery to the design of clinical studies intended to support a drug’s marketing approval.”

Natural histories “should have well-defined, carefully documented protocols” that include:

- Study duration, including date of inception and date of cutoff;
- Descriptions for how data will be collected;
- Definitions of diseases and diagnostic criteria that will be included in the study;
- A list of demographic information to be collected;
- Disease-related information, such as signs and symptoms, age at onset, diagnoses, the development of “important morbidities” and death; and
- Any regional treatment guidelines or algorithms.


FDA Reaffirms Flexibility on GCP Waiver Requests for Device Trials

The FDA last week amplified its commitment to exercising discretion when devicemakers seek waivers for new GCP requirements for device trials.

A final rule on human subject protection, which took effect Feb. 21, requires that data from medical device trials, including foreign trials, be gathered in accordance with GCPs. GCPs call for review and approval from an independent ethics committee and well-documented informed consent.

In a March 19 webinar on implementation of the final rule, the agency said it may grant waivers.
ers in cases where informed consent is difficult or impossible to obtain, such as for research on leftover human specimens and where sharing subject medical data is prohibited by local laws.

In the case of foreign clinical trials, the FDA will consider waiver requests that include:
- A statement that the trial was or will be conducted in accordance with GCP; and
- A description of the actions the sponsor or applicant took to ensure credible, accurate data and to ensure human subjects are adequately protected.

The agency issued a guidance along with the final rule outlining how to meet the agency’s requirements, request waivers and provide the required information to support clinical data submissions.

Read the guidance here: https://bit.ly/2TsK5aJ.


FDA Orders AbbVie to Stop Recruiting in Myeloma Trial After Deaths Spike

The FDA has ordered AbbVie to stop recruiting multiple myeloma patients for a Phase III trial of its anti-cancer drug Venclexta/Venclyxto, the company announced last week.

Forty-one out of 194 patients taking AbbVie’s Venclexta (venetoclax) in the company’s trial have died, the FDA found, nearly twice the percent of the patients in the trial’s placebo arm.

Venclexta already is approved for chronic lymphocytic leukemia and acute myeloid leukemia but the halt doesn’t affect any patients outside the multiple myeloma experiments, and AbbVie said it “remains confident in the benefit/risk profile” of the drug.

Patients in the Venclexta arm have met the primary endpoint with a progressive-free survival rate of 22.4 months, on average, AbbVie says. Patients in the trial who are benefiting from the Venclexta treatments have the option to stay on the medicine, AbbVie says, while the company works with regulators to address the problems.

Biogen Halts Study of Alzheimer’s Drug

Biogen and its pharmaceutical partner Eisai have announced they are halting two Phase III clinical trials of aducanumab, a drug designed to slow Alzheimer’s disease by targeting the brain-destroying protein fragments known as beta-amyloids.

Interim analysis conducted by an independent monitoring committee found that aducanumab was unlikely to benefit Alzheimer’s patients when compared to placebo. Biogen and Eisai enrolled patients with very early signs of Alzheimer’s disease to test whether aducanumab would slow the progression of brain deterioration, but results were not positive.

The failure of aducanumab is particularly discouraging as the beta-amyloid hypothesis was once the most well-accepted theory on how Alzheimer’s disease destroys the brain.

Microsoft “Bot” Matches Patients with Trials

Tech giant Microsoft is getting into the clinical trials industry, marketing a “bot” that uses AI to improve trial recruitment.

The Clinical Trials Bot — part of a suite of new healthcare-related services the company announced in February — has the capability to search for clinical trial studies as requested by either patients or clinicians for a specific disease in the hope that it will ease the process for patients to find trials that could provide otherwise unavailable medicines and therapies. Machine reading, a form of AI, is used to read and upload selection criteria for each clinical trial. Data mined is then used to determine which patients are a suitable match for the disease trial requested.

Once studies have been identified, patients are required to answer text questions to refine the list of suitable trials. The bot then suggests links to those trials that best meet patients’ needs. The bot can also be used for drugmakers to connect to test subjects.

Microsoft will not be releasing or commercializing the bot at this time, although the company is in talks with pharmaceutical companies interested in adopting the technology.

Investor-University Partnership Focuses on Novel Therapies

Healthcare investment fund Deerfield Management has committed $100 million to a new R&D partnership with Harvard University, the New York-based company announced.

The new company, called Lab1636, will be based in Cambridge, Mass., and will be headed up by Harvard’s Office of Technology Development. Organizers say they will focus on the early-stage pipeline for novel therapies in both pre-clinical and potentially even clinical trials.

The projects that will receive funding through Lab1636 will be selected by a joint advisory committee and projects “will generally focus on the development of novel therapeutics, ideally advancing many to a stage that would enable the filing of an IND application and, if successful, the commencement of clinical trials in patients,” Deerfield officials said in a news release.

AstraZeneca to Share New Cancer Research at AACR Annual Meeting

AstraZeneca will showcase the R&D progress it has made on its oncology pipeline and portfolio at the annual American Association for Cancer Research (AACR) meeting this week, the drugmaker announced.

Sharing 84 data presentations in total, the company will present headway it has made on its oncology pipeline, including 28 abstracts on new immuno-oncology data. AZ said that 33 of the presentations will focus on complementary biological pathways exploring the DNA damage response (DDR) mechanism, while 20 others will detail the company’s progress on tumor drivers and resistance mechanisms.

José Baselga, AZ’s executive vice president of research and development, oncology, said that the company also will unveil 28 new molecular entities and six combinations.
Amendments
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real issue, however, is that when we add another endpoint, there are procedures supporting it. And as we start to aggregate all those procedures it has a huge impact on performance downstream.”

For example, adding additional data points means greater demand for resources to coordinate them. Exploratory endpoints might mean more visits or more procedures per visit, which takes more time and effort not only for those who administer them, but also for trial volunteers.

More complex protocols have numerous costs, ranging from hard dollars to time to participant satisfaction. “The more complex our protocols, the worse we perform — as measured by our recruitment and retention rate [and] our cycle times — for virtually every task that we have measured,” Getz said.

The solution? Better planning in the trial design stage. Companies increasingly are turning to such solutions as:

- Protocol authoring tools that help create “a greater line of sight” between every procedure performed and the endpoint that it supports;
- Feasibility review committees that can challenge procedures not associated with essential endpoints; and
- Patient advisory boards that review draft protocols and look for ways to make participation less burdensome — one of the major factors volunteers cite in their decision not to participate.

Getz also points out that technology can help. “A number of companies are relying increasingly on the use of data, particularly electronic health and medical data, to help guide protocol design practices and determine whether eligibility criteria will make it more difficult to find study volunteers,” Getz said.

“Complexity is inevitable and as a result must be managed more prudently and strategically. It’s really all about creating better balance between the scientific objectives of the protocol and the executional objectives, which are becoming far more important for companies.”

Protocol Administration Changes

<table>
<thead>
<tr>
<th>Work Effort to Administer Protocol</th>
<th>2005</th>
<th>2015</th>
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<tbody>
<tr>
<td>Phase II</td>
<td>37</td>
<td>31</td>
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<tr>
<td>Phase III</td>
<td>62</td>
<td>50</td>
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*adapted from Medicare 1993 Relative Value Units methodology

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<tr>
<th>Total Direct Procedure Costs per Patient per Visit</th>
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<tbody>
<tr>
<td>Phase II</td>
<td>$862</td>
<td>$728</td>
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<tr>
<td>Phase III</td>
<td>$1,386</td>
<td>$978</td>
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</table>

Source: Tufts CSDD

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Presented by Kelly Smith, CCRP, Sr. Solutions Consultant for Bio-Optronics

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Clinical Trials
continued from page 1
but of dying from the treatment, which did happen to some people on this trial. I had great conversations with the immuno-oncology team and they were very clear about why I would be right for this trial. It was a choice that was made, not just based on the drug and the cancer, but very much on the patient. And that was a turning point for me — that I was being listened to and that I was going to be collaborating with a group of people who believed in me as a patient.

Q When you were approached about the trial — the informed consent process — what was the hardest thing for you to understand as people started to talk to you about what the trial entailed, etc.?

A My understanding of clinical trials was limited, and my understanding of immunotherapy was nil. I had a lot of questions and concerns and there was a lot for me to process. My oncologist did the best she could in terms of explaining treatment. My initial conversation with the immunotherapy team at Memorial Sloan Kettering was the first time that I really felt that maybe I wasn’t going to die. That maybe treatment in a clinical trial would work, but with the understanding that maybe it wouldn’t. I was in a state of desperate, deep panic. I had a conversation with someone who said that maybe participating in a clinical trial didn’t have to be a last resort for me. Maybe it could be my first resort. And that really changed the game for me.

“...that was a turning point for me — that I was being listened to and that I was going to be collaborating with a group of people who believed in me as a patient.”

—Mary Elizabeth Williams

Q How much of your information and your understanding about what the study would entail for you came from the process, this conversation you had with study team members as opposed to literally reading the paper document that you were handed?

A I had an initial meeting with a nurse. I was handed the document, and we sat down together and the expectation was that I would sign it on the spot. Even though we went through the document thoroughly, I remember feeling that I would have to sign the document whether I fully understood it or not. I also recognize that there were a lot of things that just couldn’t have been understood at that time because it was such a process and a new form of treatment, but I really struck with how vulnerable I was, how much I didn’t know and that there was such an expectation of me. And I don’t know, in retrospect, if there was a lot of understanding by the study team that I was not fully competent. I wasn’t. I was a complete mess — physically, mentally, emotionally. These decisions often need to be made under very difficult circumstances, quickly, and you do the best you can with the timeframe that you have. But I recognize now how hobbled I really was. And I don’t think that is unusual.

Q How do you believe that the informed consent form and process in a phase I trial should talk about the possibility of benefits? How should we express the truth about the odds of success in a very early study, which are low, but still leave people with hope? How can we balance that?

A That’s a very difficult question especially because in phase I trials, there is not a whole lot of expectation of success. My consent form was pretty clear about that. I felt that I had an understanding that there was a hope of success. But at that point, we were not talking about the word cure. There was no evidence of possibility that I would have all of my disease eradicated. It was really just about efficacy and potential tumor reduction. That is what was communicated to me. And the bar was set low. And my expectations were reasonable.

I’m grateful that the way it was communicated to me was, “We are going to try.” It was about time rather than about the disease. That is a smart way to approach it. Maybe this is about, “We can extend your life.” Because, ultimately, that’s really what we want. I would be happy to live with tumors if it meant I would live longer. That’s what I think most people approaching cancer now are really looking at management. So, I think that’s fine to communicate it that way.

For the rest of the interview, please go to WCG’s website: https://bit.ly/2U9qzu.
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## Drug & Device Pipeline News

<table>
<thead>
<tr>
<th>Company</th>
<th>Drug/Device</th>
<th>Medical Condition</th>
<th>Status</th>
<th>Sponsor Contact</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sutro Biopharma, Inc.</td>
<td>STR0-002</td>
<td>ovarian and endometrial cancers</td>
<td>Phase I trial initiated enrolling 160 female subjects with advanced relapsed and/or progressive ovarian, fallopian, primary peritoneal or endometrial cancer</td>
<td>sutrobio.com</td>
</tr>
<tr>
<td>Cytovation AS</td>
<td>CyPep-1</td>
<td>HPV-induced warts</td>
<td>Phase I trial initiated enrolling 58 subjects with cutaneous warts at the Centre for Human Drug Research in Leiden, the Netherlands</td>
<td>cytovation.com</td>
</tr>
<tr>
<td>Innoven Biologics, Inc.</td>
<td>IBI188</td>
<td>advanced malignant tumors</td>
<td>Phase I trial initiated in China</td>
<td>innoventbio.com/en/#/</td>
</tr>
<tr>
<td>I-Mab Biopharma</td>
<td>TJM2, a humanized immunoglobulin G1 (IgG1) targeting granulocyte-macrophage colony-stimulating factor (GM-CSF)</td>
<td>autoimmune and inflammatory diseases</td>
<td>Phase I trial initiated enrolling 32 healthy subjects in the U.S.</td>
<td>i-mabbiopharma.com</td>
</tr>
<tr>
<td>Neurovive Pharmaceutical AB</td>
<td>KL1333</td>
<td>mitochondrial disease</td>
<td>Phase Ia/Ib trial initiated enrolling healthy subjects in the UK</td>
<td>neurovive.com</td>
</tr>
<tr>
<td>Vaxart, Inc.</td>
<td>norovirus GII.4 vaccine</td>
<td>norovirus</td>
<td>Phase Ib trial initiated enrolling 86 subjects</td>
<td>vaxart.com</td>
</tr>
<tr>
<td>Infinity Pharmaceuticals, Inc.</td>
<td>IPI-549 in combination with Tecentriq and Avastin (bevacizumab)</td>
<td>front-line renal cell cancer (RCC)</td>
<td>Phase II trial initiated</td>
<td>infi.com</td>
</tr>
<tr>
<td>Infinity Pharmaceuticals, Inc.</td>
<td>IPI-549 in combination with Tecentriq and Abraxane (nab-paclitaxel)</td>
<td>front-line triple negative breast cancer (TNBC)</td>
<td>Phase II trial initiated</td>
<td>infi.com</td>
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<tr>
<td>Imugene Limited</td>
<td>HER-Vaxx (IMU-131)</td>
<td>HER-2 positive gastric cancer</td>
<td>Phase II trial initiated enrolling 68 subjects with metastatic gastric cancer overexpressing the HER-2 protein at multiple sites across Asia, Eastern Europe and India</td>
<td>imugene.com</td>
</tr>
<tr>
<td>ImmunogenX</td>
<td>Latiglutenate</td>
<td>celiac disease</td>
<td>Phase II trial initiated enrolling subjects at the Mayo Clinic in Rochester, MN</td>
<td>immunogenx.com</td>
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</table>

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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<table>
<thead>
<tr>
<th>Company</th>
<th>Drug/Device</th>
<th>Medical Condition</th>
<th>Status</th>
<th>Sponsor Contact</th>
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</thead>
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<tr>
<td>Xeris Pharmaceuticals, Inc.</td>
<td>ready-to-use, room-temperature stable liquid glucagon</td>
<td>Type 1 diabetes</td>
<td>Phase II trial initiated enrolling 48 subjects with Type 1 diabetes who experience episodes of exercise-induced hypoglycemia (EIH) who receive daily insulin treatment via a subcutaneous infusion pump</td>
<td>xerispharma.com</td>
</tr>
<tr>
<td>Via Surgical Ltd.</td>
<td>FasTouch Absorbable Fixation System</td>
<td>soft tissue repair</td>
<td>510(k) clearance granted by the FDA</td>
<td>viasurgical.com</td>
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<tr>
<td>Aptar Pharma</td>
<td>Bidose nasal spray device</td>
<td>depression</td>
<td>Breakthrough Therapy designation granted by the FDA</td>
<td>aptar.com/pharma</td>
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<tr>
<td>Aimmune Therapeutics, Inc.</td>
<td>AR101</td>
<td>peanut allergy</td>
<td>BLA approval granted by the FDA</td>
<td>aimmune.com</td>
</tr>
<tr>
<td>Allergan plc</td>
<td>AVYCAZ (ceftazidime and avibactam)</td>
<td>complicated intra-abdominal infections (cIAI) in combination with metronidazole and complicated urinary tract infections (cUTI) in pediatric patients three months and older</td>
<td>sNDA approval granted by the FDA</td>
<td>allergan.com</td>
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<tr>
<td>Genentech</td>
<td>Tecentriq (atezolizumab) in combination with carboplatin and etoposide (chemotherapy)</td>
<td>extensive-stage small cell lung cancer (ES-SCLC)</td>
<td>Approval granted by the FDA</td>
<td>gene.com</td>
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<tr>
<td>Sage Therapeutics, Inc.</td>
<td>Zulresso (brexanolone) injection</td>
<td>postpartum depression (PPD)</td>
<td>Approval granted by the FDA</td>
<td>sagerx.com</td>
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<tr>
<td>Regeneron Pharmaceuticals, Inc. and Sanofi</td>
<td>Dupixent (dupilumab)</td>
<td>adolescent patients 12 to 17 years of age with moderate-to-severe atopic dermatitis whose disease is not adequately controlled with topical prescription therapies, or when those therapies are not advisable</td>
<td>Approval granted by the FDA</td>
<td>regeneron.com</td>
</tr>
</tbody>
</table>
## CWMarketPlace

CWMarketPlace is a monthly section featuring a range of clinical research service providers who have Industry Provider Profile pages posted on CenterWatch.com. Included in their annual subscriptions, company profiles are randomly selected to appear in this section, providing added exposure for their products and services. To learn more about becoming an Industry Provider Profile page subscriber, contact Sales at (617) 948-5100 or sales@centerwatch.com. Click on any provider to view the company’s complete online profile or click here to search more profiles.

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