Drug shortages may derail careers along with trials

In virologist Dirk Dittmer's lab at the University of North Carolina–Chapel Hill, there are two silent rooms. One contains a hulking, quarter-million-dollar robot, custom-made to analyze blood samples; the other contains a small protein-synthesis machine. Most days, scientists don't enter either room. The machines sit there gathering dust while Dittmer's team waits on a massive clinical trial in African patients with AIDS to begin—a trial that has been delayed indefinitely due to drug shortages.

The issue of drug shortages has posed a growing problem for doctors and patients in the US. In the first eight months of this year, for instance, the country's Food and Drug Administration (FDA) recorded nearly 200 such shortages, in contrast to the 178 shortages reported in 2010 overall. As a result, hundreds of clinical trials hang in the balance, and the delays are jeopardizing the careers of many clinical investigators.

One person on Dittmer's research team facing a career dilemma is graduate student Kristen Tamburro, who received a prestigious Howard Hughes Medical Institute fellowship in September 2009. Tamburro joined Dittmer's lab to pursue translational medicine, tempted by the promise of data from the AIDS trial—which aimed to test Janssen's Doxil (doxorubicin), currently approved to treat ovarian cancer and multiple myloma, in patients with AIDS who have developed the deadly cancer Kaposi's sarcoma. Halfway toward obtaining her PhD, when the trial remained on standby, she realized she needed a new plan.

"Since the samples won't come in before I graduate, the project has been removed from my thesis," she says. Although she analyzed several small, observational trials to salvage her thesis, a trial of this magnitude and scale could have transformed her career. "It would have been a great experience to have had," she says.

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Another paused phase 3 trial aims to treat acute myeloid leukemia (AML) in the elderly. It is waiting for the chemotherapy drugs Cerubidine (daunorubicin), manufactured by Winthrop Pharmaceuticals, and Tarabine PFS (cytarabine), made by several companies, including Hospira. James Foran, a medical oncologist at the Mayo Clinic in Jacksonville, Florida, heads the study. The trial is his baby—he started working on it five years ago and was hoping to have preliminary data in 2013. "This is the sort of trial that can get me promoted to professor someday," he says. "If it fails, I will have to go straight back to the drawing board."

Foran is frustratingly close to success. "If the treatment works, it will be one of the biggest steps forward in two decades for elderly acute myeloid leukemia," he says. "But I am concerned the delay will dilute the impact of the study, or that somebody else will answer the question first."

In Ari Melnick's laboratory at the Weill Cornell Medical College in New York, the fate of many projects hinge on the outcome of Foran's clinical trial. Melnick wants the DNA of participants in Foran's study. So far, trial participants have not been enrolled because of the lack of the chemo drugs; by domino effect, Melnick has not received any DNA samples.

Once he gets his hands on the samples, he will analyze newly identified gene mutations to see whether they can act as markers of relapse or progression of AML. "There are postdoctoral fellows here whose livelihoods depend on this work," says Melnick. The delay could result in "these people's careers being derailed."

Melnick is also worried about research funding. Right now, he is applying to the US National Institutes of Health for support. But usually when trials are stuck, it's likely that grants won't come in either. "It all falls apart," he says.

Madhumita Venkataramanan

Research organizations push back against clinical trials directive

LONDON — European legislation intended to streamline clinical research is so steeped in bureaucracy that it is threatening "the development of potentially lifesaving treatments," says a consortium of 16 research organizations, including Cancer Research UK, the Wellcome Trust and the UK's Academy of Medical Sciences.

In late September, the consortium issued a statement calling on the EU to include changes that would cut red tape and streamline the authorization of clinical trials as part of its planned revision to its European Clinical Trials Directive (ECTD) in early 2012.

Instead of smoothing the process, "the directive has increased the administrative burden and cost of clinical trials, with no evidence of discernible benefits to patient safety or to the ethical soundness of trials," John Bell, president of the Academy of Medical Sciences, told *Nature Medicine*.

The measure, which came into force in 2004, has been plagued by concerns from the outset. In 2008, the EU promised to re-assess the directive's impact and to make legislative changes "if needed" in 2012.

Ironically—given the directive was meant to standardize the monitoring and regulation of trials across member states—it is being interpreted differently in each country, making multicenter trials virtually impossible, the consortium's statement says.

The eagerness to harmonize processes has led to an ineffectual one-size-fits-all approach that has left researchers drowning in red tape. For instance, all trials are subject to excessively cautious protocols so that trials of well-known drugs are regulated as stringently as those of completely new drugs.

Traditional large-scale clinical trials can also lack the flexibility that modern medicine requires, says Marie-Cécile Le Deley, at the Institut Gustave-Roussy in Villejuif, France. Le Deley, who presented data from simulating different trial designs at the 2011 European Multidisciplinary Cancer Congress in Stockholm in September, found that for rare cancers, which by definition have small numbers of affected individuals, lengthy large-scale trials "may be counter-productive."

What is needed instead, says Mark Walport, director of the Wellcome Trust, is "regulation that is proportionate to the risks" involved. For example, says Bell, "The UK Medicines and Healthcare products Regulatory Agency has developed guidelines in the UK that are currently being trialed and could be used to inform a proportionate approach in the EU."

A 2008 study showed that, on average, approvals in Europe took 67 days compared with 15 days in the US for the same global drug trial (*Br. J. Clin. Pharmacol.* **66**, 546–550, 2008). Walport says delays such as these "make Europe less competitive internationally, resulting in industrial and academic groups moving to other countries in the world to undertake their research."

Priya Shetty