principal investigator at the clinical trial site California Neuroscience Research Medical Group in Sherman Oaks, California, who co-chaired the ISCTM workshop. Alarmed by the number of subjects popping up in multiple studies he ran, Shiovitz began in 2011 to compile a database of people who enroll or go through screening with his drug sponsor clients and at other nearby trial sites.

Earlier this year, one man who came to enroll in a new schizophrenia study was flagged as a duplicate; he had visited at least seven trial sites in the last 12 months. He admitted that his strategy was to enroll in several schizophrenia trials, but take only the pills that made his head feel clearer. Either way, he got a stipend for participation, and reported to each trial that he was taking only the prescribed drug, in regular doses.

Shiovitz encourages his sponsors to prescreen for these duplicate subjects, which he estimates to make up 5% to 10% in trials for central nervous system drugs. "Scientists often don't take into account when they design their elegant studies that the subjects are real people who act in their own interest, for money or to feel better," Shiovitz says. Producing good, clean data for the investigators is "not their goal."

Some investigators are trying to track the very act of taking a drug, embedding in each pill a microchip that sends a wireless signal to a wearable device when ingested. One system, developed by Proteus Digital Health, has approval from the U.S. Food and Drug Administration and will be made commercially available this month.

But once enrolled, these nonadherent subjects can't simply be excluded from the post-trial analysis, says Craig Mallinckrodt, a statistician at Eli Lilly in Indianapolis and a member of the ISCTM working group on nonadherence, which plans to put out a white paper on the problem by 2016. Ignoring those people could create a bias of its own, because they may also be the ones who have negative effects from the drug. "At the end of the day," Mallinckrodt says, "you can only speculate about what would have happened had the patients adhered."

A 2010 report from the National Academies' Committee on National Statistics encouraged investigators to think about strategies that may help well-intentioned trial participants stick to a drug regimen. Shorter trials with less complicated dosing instructions could help, for example.

Stanford's Blaschke suggests much could be gained by better communicating the purpose of the trial, and the importance of following through with medication. Although databases and surveillance can spot the offenders, he says, "many of us feel that the problem is much bigger than that." ■

INFECTIOUS DISEASES

Ebola vaccine trials raise ethical issues

Randomized studies may offer fastest answer

By **Jon Cohen** *and* **Kai Kupferschmidt**

Come January, as many as 20,000 doses of an Ebola vaccine candidate may be ready for testing in the unprecedented epidemic racing through West Africa. The vaccine—and another one whose development is 6 weeks behind—could bring hope to a desperate, panicked population. Indeed, some scientists believe that the epidemic has grown so large that vaccines will be essential to stopping it. But difficult questions are now emerging about how to design clinical trials, who should be the first to get the shots, and when to begin mass production.

> ***"I suddenly saw a real double-blinded trial with another vaccine as the control was the way to go."***
>
> **Ira Longini,** University of Florida

Until recently, many scientists said that with Ebola, it wouldn't be ethical to use the standard procedure for testing a vaccine's efficacy: so-called randomized controlled trials (RCTs), in which some trial subjects are assigned to a control group that doesn't receive the actual vaccine. At a consultation held by the World Health Organization (WHO) on 29 to 30 September, however, there was unexpectedly broad support for the RCT design after all—but not from Doctors Without Borders (MSF), which is playing a huge role in the current outbreak.

On 2 September, one of the vaccines, made by pharmaceutical giant GlaxoSmithKline (GSK) of Rixensart, Belgium, in collaboration with the National Institute of Allergy and Infectious Diseases (NIAID), entered phase I trials, which test safety and immune responses in a small number of healthy volunteers. Preliminary results could be available as early as November. Similar studies for the other vaccine, developed by the Public Health Agency of Canada and produced by NewLink Genetics in Ames, Iowa, were launched 13 October, with early results expected in December.

If the vaccines do not cause harm and trigger the immune response scientists hope to see, WHO has recommended jumping straight into what amount to phase III efficacy tests in Liberia, Guinea, and Sierra Leone, the three hard-hit countries. It's an extraordinary, unprecedented gamble to move so quickly—but one that WHO consultants say is warranted by Ebola's extreme threat.

In RCTs, half of the participants are randomly assigned to receive the experimental shot and the other half a dummy, or placebo; ethicists say that's OK if it's unclear whether the vaccine will help, do nothing, or cause harm. If significantly more people in the placebo arm develop disease, the vaccine works. But animal experiments suggest the Ebola vaccines could well offer protection; keeping them from workers facing a disease as deadly as Ebola is unethical, some say.

The leading alternative is a trial design known as stepped-wedge, which takes advantage of the inescapable reality that a large-scale study can't give everyone the vaccine on the exact same date. Stepped-wedge trials compare the rates of infection in people already vaccinated with those who have yet to receive the shots. "People are more comfortable" with this setup because everyone in such a study gets the Ebola vaccine, says Barney Graham, a virologist at NIAID in Bethesda, Maryland, who attended the WHO meeting.

But at the meeting, Ripley Ballou, who heads the Ebola vaccine project for GSK, argued for an RCT—although the placebo would be replaced with an "active control," a proven vaccine (for instance, against hepatitis B) that would at least protect participants against another virus. An RCT, Ballou argued, offers the fastest, most acceptable route to determining whether a vaccine is safe and effective, and thus would potentially save the most lives.

Ballou described a randomized study in which 2500 people, probably health care workers, would receive the vaccine and 2500 an active control. He stressed that his team at GSK had many unknowns to wrestle with, including health care workers' infection risk, which they estimated at 10% per year spent in contact with Ebola patients. Assuming this is correct, and that the vaccine works at least 80% of the time, researchers could be "absolutely confident" about efficacy after 30 infections, which would likely

occur within 3 months, Ballou says. A vaccine that had 60% efficacy could still yield an answer with fewer than 60 infections.

That's much faster than a stepped-wedge design, he contends. Such a study would enroll participants at the same point in time, but would stagger distribution of vaccine, say, to different Ebola treatment units. But researchers would still have to observe the different communities from the same start date, introducing delays and making it harder to tell whether the vaccine works. Infection rates might change over time, too, complicating the analysis.

Ballou didn't win over MSF. "Studies on efficacy in affected countries and more so in at-risk populations should not have a placebo or active control arm as this cannot be defended ethically," says Annick Antierens, a meeting attendee who oversees experimental Ebola products for MSF. Antierens says MSF would support other Ebola vaccine efficacy trial designs, but would not specify which ones. One idea is to just distribute vaccine to health care workers and then do an "observational" study that does not have a control group but compares vaccination status in those who became ill to those who did not.

But most meeting participants sided with Ballou, says Ira Longini, a biostatistician from the University of Florida in Gainesville. Longini changed his planned talk on the stepped-wedge design after Ballou spoke. "I suddenly saw a real double-blinded trial with another vaccine as the control was the way to go," he says. Marie-Paule Kieny, a WHO assistant director-general, says "the meeting was quite tense at moments," but that there ultimately was "broad agreement" on this design. "Rip's study made sense," Kieny says.

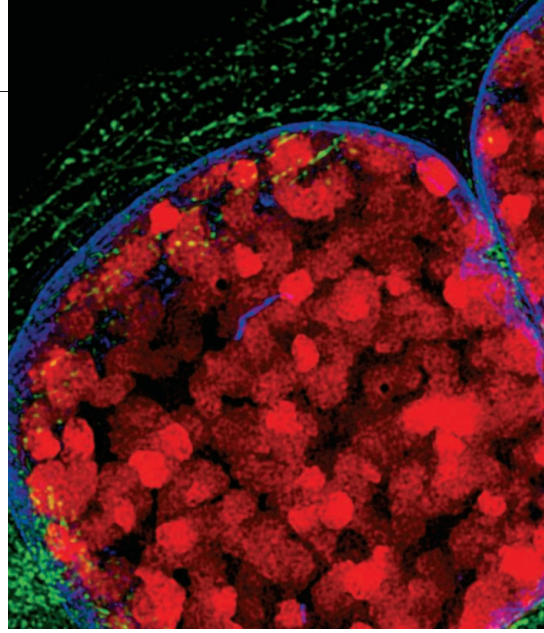
Jeremy Farrar, an infectious disease researcher who heads the Wellcome Trust in London, cautions that people on the front lines of Ebola may disagree. An RCT may yield results faster, but if it's simply unacceptable for trial participants, a stepped-wedge design is preferable. "If you were there tomorrow and you were a health care worker, would you be willing to be in a control arm, when the next 3 months you will be looking after patients with Ebola?" Farrar asks. "I don't want us to have months of discussions about the best way of handling this."

The 20,000 doses of the GSK vaccine that may be ready by January—double earlier projections—could be enough for several trials, which might allow different groups of participants to enroll in different designs. "I would do all these trials simultaneously," Longini says.

Before the trials are launched, health officials also need to decide who should participate. An August WHO consultation recommended that efficacy trials first recruit health care workers, as they are at high risk and provide a critical service. But the latest meeting "stopped talking about health care worker and started talking about front-line caregiver," Ballou says, which means everyone from doctors and nurses to janitors, people who collect the bodies, and gravediggers.

The next issue is when to scale up production. Many researchers, including Longini, argue that massive production of Ebola vaccines should begin as soon as positive phase I data exist, to increase the likelihood that shots will be widely available when the evidence from the phase III study comes in. "I'd pull out all the stops," Longini says. "I'd try to make 30 to 40 million doses to cover at-risk West African populations." Farrar agrees. "We may come to regret that we have to throw those vaccines away if they prove not to be effective," Farrar says, "but I think that is a risk we have to take." ■

Liberian nurses pick up a dead body from the waiting area of a hospital in Monrovia.



NOBEL PRIZES

Light loophole wins laurels

Chemistry prize winners pushed microscopes past supposed limit

By **Daniel Clery**

For more than 100 years, microscopists were stymied by a law of nature—or so they thought. The so-called diffraction limit meant that optical images could never reach a resolution finer than half a wavelength of light, and the fine details of living things would be forever blurry. Then, beginning in the late 1990s, three scientists found a way to blast through that limit. Their techniques, all based on getting the specimen itself to absorb and emit light, have won them this year's Nobel Prize in chemistry.

Microscopists told *Science* they are delighted about the award, announced on 8 October, which went to Eric Betzig of the Howard Hughes Medical Institute in Ashburn, Virginia; Stefan Hell of the Max Planck Institute for Biophysical Chemistry in Göttingen, Germany; and William Moerner of Stanford University in Palo Alto, California. "It's very well deserved," says Michelle Peckham, a cell biologist at the University of Leeds in the United Kingdom and a council member of the Royal Microscopical Society. "It's opened up the horizons of microscopy to new techniques, especially in the biological sciences."

The so-called Abbe diffraction limit had condemned things smaller than about 0.2 micrometers—including bacteria, cel-

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