On 2 October, Ashoka Mukpo left his father a voice mail from Monrovia, saying he had “unwelcome but not unexpected news.” Mukpo, an American freelance cameraman for NBC News, had tested positive for Ebola virus. Mukpo’s father, Mitchell Levy, a pulmonologist who heads critical care at Rhode Island Hospital in Providence, immediately helped arrange his son’s transfer to the Nebraska Medical Center in Omaha, one of four specialized Ebola centers in the United States.

The big question then was how to treat the patient.

The medical team, which included Levy, planned to intensively monitor Mukpo and give him intravenous replacement of fluids and electrolytes, antibiotics to combat secondary infections, and drugs to slow diarrhea and vomiting. But it also had three unproven treatments available. TKM-Ebola, which inhibits viral RNA, has worked beautifully in monkeys, the best animal model. Kent Brantly, a missionary doctor in Liberia who developed Ebola and recovered, offered to donate plasma removed from his blood, which contained antibodies that might help. And there was brincidofovir, a drug being developed for other viral infections that has been shown to stop Ebola virus in test tubes. (The most famous drug candidate, ZMapp, was not available at the time.)

After careful consideration, Mukpo and his doctors opted to use the serum—a proven intervention with other viruses—and brincidofovir, which has a substantial safety record. But they decided to forgo TKM-Ebola, despite its promise, because of worries that it could trigger overproduction of cytokines, a dangerous inflammatory response also caused by the Ebola virus, and scant data from human trials. “I was not quite on my deathbed and didn’t need to take any huge risks,” Mukpo says. His doctor father had reached a similar conclusion. “I didn’t have a high degree of confidence that brincidofovir was going to work, but I was loath to try an investigational agent with no data,” Levy says.

Mukpo survived, but no one has any idea whether the experimental treatments helped him, did nothing, or even slowed his
recovery. The same is true for Brantly and 17 other Ebola patients who received experimental interventions in the United States and Europe. (One other Ebola patient was treated in Germany without any experimental interventions.) Many, like Mukpo, were given several treatments at the same time, making it hard to unravel the impact of any one of them. The fact that they were taken care of in modern, well-staffed hospitals may also help explain why 75% have survived (see sidebar, p. 911). “Probably the best we can say is that the experimental treatments are not killing anyone,” says Michael Kurilla, who heads the Office of Biodefense Research Resources and Translational Research at the National Institute of Allergy and Infectious Diseases (NIAID) in Rockville, Maryland.

Now, that’s about to change. As early as next month, researchers will begin trials in West Africa to find a solid answer to the key question: Do the treatments work? Carried out in makeshift emergency hospitals by researchers wearing full protective gear in the middle of a deadly epidemic, these will be some of the most unusual drug trials ever done. And they also raise major ethical and practical questions, some of which were intensely debated at a World Health Organization (WHO) meeting in Geneva, Switzerland, on 11 and 12 November.

Perhaps the most important one: Is it right to do randomized controlled trials (RCTs), in which some people don’t get the novel intervention? Doctors Without Borders (MSF), which has led the medical response to the outbreak, says no—not with a disease as deadly as Ebola. Instead, on 13 November MSF said it will take part in three trials that will use an alternative design in which everyone who enrolls receives the untested treatment. But others argue that such setups may not give clear answers and squander a precious scientific opportunity.

It’s an uncomfortable and complex debate held under extreme time pressure. “Everyone has stepped outside of their comfort zone in a big way,” says Peter Horby of the University of Oxford in the United Kingdom, who is leading one of the upcoming trials and attended the WHO meeting.

UNTIL THE CURRENT EPIDEMIC began, development of Ebola treatments was painfully slow. Since the first recognized outbreak in 1976, the virus has surfaced two dozen times, but until 2014, it had sickened fewer than 2500 people altogether. That didn’t make for an attractive market for private companies, leaving most research to be funded by the U.S. government, which worries that hostile nations or bioterrorists may stage gruesome attacks with the virus. And because traditional containment efforts have stopped every outbreak to date over a few months, researchers have had few opportunities to test novel treatments.

Among the candidates, the two front-runners are TKM-Ebola, an RNA inhibitor of the virus packaged in a lipid nanoparticle, and ZMapp, a laboratory-made cocktail of three Ebola antibodies that shot to fame in August when it was given to Brantly. (A breathless CNN report called it a “secret serum that likely saved his life.”) These drugs have worked better than all others in monkey studies, which puts them “light-years ahead” of other treatments, says Thomas Geisbert of the University of Texas Medical Branch in Galveston, who conducted many of the key experiments. “If I were exposed to Ebola I’d take ZMapp or Tekmira’s drug and I wouldn’t worry,” he says.

“Everybody keeps talking about ZMapp,” says Annick Antierens, who heads work on investigational Ebola drugs at MSF in Geneva. But both ZMapp and TKM-Ebola are relatively difficult to make, and despite aggressive efforts to ramp up their production, fewer than a thousand doses of each may be ready by the end of the year. Both are also difficult to test in the affected countries, as they require intravenous infusions.

Other candidates are more easily manufactured and administered—but the data supporting their use are weaker. Brincidofovir was designed to interfere with viral DNA replication, and it’s now in ongoing phase III trials against cytomegalovirus and adenovirus infections; about 1000 people have received it. This spring, Chimerix, the manufacturer, had two outside labs test the drug against Ebola; they found that the drug did indeed inhibit the virus in test-tube studies. Brincidofovir cannot be tested in monkeys because an enzyme in the animals rapidly inactivates the drug, but Chimerix says studies in guinea pigs and mice are ongoing.

Another option is favipiravir, an influenza drug licensed in Japan that protected mice from Ebola when administered 6 days after they were exposed to the virus. But unlike monkeys, mice only develop mild disease from Ebola strains, so the experiment relied on a mouse genetically engineered to lack immune defenses against viruses. That makes the result harder to interpret.

Antibody-containing whole blood or the plasma component could theoretically be harvested from thousands of recovered Ebola patients, but “convalescent serum” has not worked well in monkey experiments. One published report shows that seven out of eight people who received whole blood from survivors during a 1995 Ebola outbreak in the Democratic Republic of the Congo survived, but they were treated late in the course of disease, and some researchers believe they likely would have recovered without the serum. A horse serum that contains Ebola antibodies is being developed, too.

Drugs that target only Ebola symptoms, rather than the virus itself, might also help. Doctors in Germany, for instance, have treated two patients with an experimental treatment named FX06 that aims to stop fluid leaking from blood vessels, a major problem in patients with advanced Ebola infections. One of the patients recovered, the other died.

Many other ideas have been floated. Kurilla is setting up a database for WHO to publish negative findings to discourage researchers from pursuing compounds that don’t pass muster in screening assays or animal experiments. “We are getting inundated with people who are suggesting the same thing over and over again,” he says. A doctor in Liberia in particular has received widespread attention for touting the HIV drug lamivudine, but there is zero evidence from lab tests that it has anti-Ebola activity.

NOW RESEARCHERS HAVE an unprecedented chance to test candidate treatments systematically. At last week’s WHO meeting in Geneva, researchers who want to con-
duct clinical trials for Ebola treatments met with regulators, pharmacologists, and representatives from the three most affected countries to work out how to move from anecdotes to hard evidence—and which drugs to test. More than 120 products have been put forward as possible treatments, but far too few clinics are qualified to participate in trials, the attendees were told. And given the lack of supply, ZMapp and TKM-Ebola are not on the table for the moment. Instead, the less promising treatments are moving ahead first.

An international consortium led by Johan van Griensven of the Institute of Tropical Medicine in Antwerp, Belgium, plans to test convalescent serum in Conakry, the Guinean capital. The French biomedical research agency INSERM will lead a trial of favipiravir in Guéckédou, Guinea. And brincidofovir will be put to the test in a study led by Oxford, in either Sierra Leone or Liberia. The three clinical trials will share a simple form to collect the most basic of data; recording anything is exceedingly cumbersome when health care workers are wearing bulky personal protective gear.

The ethical issues surrounding the trials have roiled the scientific and humanitarian community—and were “vigorously debated” at the meeting, according to WHO. MSF has said that for the moment it won’t participate in trials that randomly decide who would receive the treatment. “If an outbreak like this with such a high fatality rate would be happening in Europe, I don’t think randomizing patients would be acceptable,” says MSF’s Antierens. “I certainly would not want to get standard of care if there is a promising drug available.” A much discussed editorial published online on 10 October in *The Lancet*, signed by prominent ethicists and scientists from 11 countries, made the same point. Some worry that RCTs could even trigger protests and violent reactions from the families of patients and their communities.

But others say trials without an untreated control group raise ethical problems of their own. “I don’t know whether these agents might be harmful, and given a disease with mortality as high as this one, you might not be able to detect that harm” without a control arm, says Clifford Lane, clinical director at NIAID in Bethesda, Maryland. RCTs also reduce confusion introduced by variables such as how sick people are when treatment begins and whether patients in a trial also receive better care. Randomization, Lane says, is the only effective way to “make sense of anything.”

The three studies that will start first, all at MSF centers, will not have a randomized design. Instead, all patients will get the treatment; their survival rate 14 days later will be compared with survival in earlier patients who didn’t receive the treatment. (The convalescent serum trial will also have a “concurrent” control arm that eludes the ethical problems: Some patients won’t be treated because there is no donor with a matching blood type.)
Antierens agrees that such trials may not detect small effects of a drug, but says the goal is to determine whether an intervention is worthless or clearly works. “We are not interested in whether some liver enzymes are a little bit higher,” she says. “We are looking for a significant change in survival.” For the brincidofovir trial, for example, the researchers have agreed to define survival below 50% as “failure” and above 80% “success.” If the data are ambiguous, an RCT could be considered, she adds.

The horrific nature of the epidemic has led to other arrangements rarely seen in clinical studies. The researchers conducting the favipiravir study initially wanted to target adults within the first 2 days of their illness. MSF asked for the design to be changed so no one would be refused the drug—including people who have been sick longer and children. “People from the field said, ‘What are we going to do when a family arrives? We treat the parents and not the child?’” says Xavier de Lamballerie of Aix-Marseille University in France, who is leading the study. The brincidofovir study will enroll up to 140 people, and at MSF’s request it will continue offering the drug while data from the trial are being analyzed to make sure that no patient misses out on a potentially effective treatment.

**PROPONENTS OF RCTS** are aggressively pushing ahead with trial plans, too. Luciana Borio of the U.S. Food and Drug Administration in Silver Spring, Maryland, who attended the WHO meeting; NIAID’s Lane; and others have developed a protocol that would test multiple interventions—including ZMapp and TKM-Ebola—in a single large RCT, using sophisticated Bayesian statistics to get an answer as fast as possible. Lane is now negotiating with the Liberian government about setting up several of these studies. Liberia is not opposed to RCTs, says Stephen Kennedy, an investigator at the University of Liberia–Pacific Institute for Research and Evaluation Africa Center in Monrovia, who advises the country’s ministry of health about its oversight of Ebola clinical research. “We have to use the gold standard,” Kennedy says. “We understand the issues and know what is appropriate for Liberia.”

Borio well understands the concerns about randomization, but says that not getting a clear answer would be worse. The nonrandomized trials announced last week have a “significant risk of not generating interpretable data,” Borio says. “It is so important to get this right. It’s important for patients who will become affected during this epidemic, and also for generations to come, since future outbreaks will surely occur.”

A room reserved for Ebola patients at the University Medical Center Groningen in the Netherlands.

**Saving lives without new drugs**

When people from the United States and Europe working in West Africa have developed Ebola, time and again the first thing they wanted to take was not an experimental drug. It was an airplane that would cart them home.

Care for Ebola patients in Liberia, Sierra Leone, and Guinea varies greatly at different clinics, but it never matches what wealthy countries provide. This partly explains why the Ebola epidemic has had a case fatality rate (CFR) of 70%, according to World Health Organization calculations. Too few Ebola patients have been treated outside Africa to make scientifically valid comparisons—and they may have been healthier before falling ill—but only five out of 20 to date have died, a CFR of 25%.

Now, there’s a push to improve care in West Africa. Just a handful of basic interventions to fight the killer effects of Ebola, including dehydration and secondary infections, could dramatically lower the CFR there, says Michael Callahan, an infectious disease specialist at Massachusetts General Hospital in Boston. A case in point appeared online on 5 November in *The New England Journal of Medicine* (NEJM): Relatively intensive care in Conakry led to a CFR of 43%.

With so much room for improvement in supportive care, the current international focus on drugs is “misguided,” says Callahan, who has recently worked in Monrovia and provided care in four previous Ebola outbreaks. “While we wait for months for forthcoming experimental therapies, many lives can be saved, certainly hundreds and possibly thousands, using inexpensive and simple therapies,” he says.

Callahan is helping an international team develop guidelines dubbed Maximum Use of Supportive Therapy (MUST), aimed at keeping more patients alive. It includes intravenous (IV) drips to replace massive fluid loss from diarrhea and vomiting, a risk factor for shock; balancing of electrolytes such as calcium or potassium, which prevents kidney and heart failure; nasogastric tubes for feeding; and testing and treatment of secondary infections such as malaria. Introducing MUST will also make it easier to study new treatments, Callahan says: Randomized controlled trials—ethically fraught because only some patients get the novel treatment (see main story, p. 908)—will be much more acceptable if everyone receives high-level care. In addition, MUST might reveal side effects of new drugs that would otherwise be masked by Ebola symptoms, and it could reduce the rate of complications that might be incorrectly blamed on a drug.

It’s an important proposal, but Ebola clinics will need more resources to offer MUST, says John Fankhauser, an American clinician who has worked at the ELWA hospital in Monrovia since before the outbreak surfaced. Overwhelmed by patients and logistical challenges, many clinics have provided minimal supportive care. “We are able to give IV hydration, but the testing is limited to malaria and Ebola,” Fankhauser says. Tests for electrolytes and other types of monitoring MUST calls for are simply beyond reach, he says. Callahan says the additional measures cost less than $600 extra per patient at a Monrovia clinic in August.

Armand Sprecher of Doctors Without Borders (MSF) in Brussels, who co-authored the *NEJM* report, concedes that the standard of care dropped when Ebola exploded this summer. But Sprecher, who is “very supportive of supportive care,” says MSF clinics have corrected several problems and now doubts that MUST can save many more lives. “I’m less optimistic than some people about how much of an effect we’re going to have,” he says. “I hope I’m wrong.”
A dose of reality
Jon Cohen and Kai Kupferschmidt

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