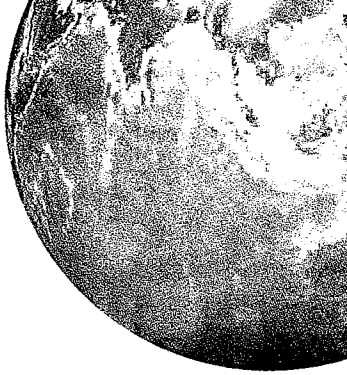

Ethical Issues in International Biomedical Research

A CASEBOOK

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Case 9

Pharmaceutical Research in Developing Countries

Testing a New Surfactant in Bolivia

Background on Bolivia

Located in central South America, Bolivia is surrounded by Peru, Brazil, Paraguay, Argentina, and Chile. It is one of the least developed countries in South America. About two-thirds of the population lives below the poverty line, many as subsistence farmers. The country is not densely populated, and the annual population growth rate is around 1.76%.

Consistent with income disparities, 21% of the population is undernourished and 15% lack access to improved water sources. Nonetheless, life expectancy in Bolivia has increased from 46.7 years in 1975 to 63.9 years in 2005. Infant and child mortality rates have also improved dramatically over the last 30 years, yet infant mortality remains relatively high at 53 per 1,000 live births and mortality rate for children under 5 is now 66 per 1,000 children. Overall, approximately 7% of the GDP goes to health care with about 4.2% of GDP for public spending on health care. Health care spending is approximately US $180 per capita (in purchasing power parity).

Bolivia has experienced significant political instability since its independence from Spain in 1825. Democratic civilian rule, established to a limited degree in the 1980s has been challenged by difficult problems of deep-seated poverty and social unrest. However, commerce with neighboring countries is growing because of Bolivia's membership in the Andean Community, which guarantees free trade with other member countries—Peru, Ecuador, Colombia, and Venezuela.

Respiratory Distress Syndrome and Surfactants

Respiratory distress syndrome, or RDS, is a common and potentially fatal disease in premature infants that is caused by insufficient surfactant in the lungs. Surfactant is

a protein that reduces alveolar surface tension, enabling proper lung inflation and aeration. In most full-term infants, surfactant ensures soft and pliable lungs that stretch and contract with each breath. Premature infants have underdeveloped lungs with insufficient surfactant and consequently their lungs are stiff and do not inflate as easily. As a result premature infants are more likely to have RDS.

RDS in infants is ideally treated by general supportive care, including intravenous fluids and mechanical ventilation and the administration of surfactant. The use of surfactant replacement therapy as the standard treatment for RDS in the Western world has produced a 34% reduction in neonatal mortality in randomized trials.[1] But surfactant does not effectively treat all RDS. Consequently, RDS remains the 4th leading cause of infant mortality in the United States and is responsible for up to half of all infant mortality in developing countries, where access to surfactant therapy or ventilator support is limited.

Surfactant therapy has been approved for use in Latin America, but its high cost, about US$1,100–2,400 per child, precludes it as a viable option for most infants in Latin America, where per capita annual health spending ranges from US$60–$225. In Bolivia, Ecuador, and Peru, where only a privileged minority has access to surfactant therapies and adequate prenatal monitoring, RDS continues to be responsible for at least 30% of neonatal deaths.

Surfactant Drug Trials and Regulatory Approvals in the United States

Since 1990, the U.S. Food and Drug Administration (FDA) has approved four surfactants for either the prevention or the treatment of RDS in premature infants. The first, Exosurf, is a synthetic product that was approved in 1990 for the prevention of RDS in infants with birth weights less than 1350 grams, and for treatment of heavier infants with evidence of incomplete lung development and/or RDS. The FDA based its approval for these uses on the results of placebo-controlled trials. In these trials, all children received mechanical ventilation. Infants in the intervention arm received Exosurf through the ventilator in a spray form, while children in the "placebo" control group received a spray of air.

In 1991, the FDA approved a new surfactant drug derived from cow lung surfactant, called Survanta, for the prevention and treatment of RDS in premature babies weighing between 600 grams and 1700 grams. Approval of Survanta was also based on the results of placebo-controlled prevention and treatment trials. A third surfactant, Infasurf, was approved in 1998 on the basis of its superiority to Exosurf on various clinical measures in 2 separate trials, one for the treatment of RDS and one for prophylaxis of RDS. A treatment trial for RDS comparing Infasurf to Survanta, however, showed no significant difference on major efficacy parameters. In a comparative randomized trial for the prevention of RDS in premature infants less than 30 weeks gestation, more infants died on Infasurf than on Survanta. Despite its inferiority to Survanta, Infasurf was approved for the prevention of RDS in premature infants less than 29 weeks of age.[2] None of these Infasurf trials involved a placebo arm.

One subsequent surfactant, Curosurf, was approved by the FDA in 1999 for the treatment of RDS on the basis of 2 trials. One trial compared single versus multiple dose Curosurf, and the 2nd compared single-dose Curosurf to disconnection from mechanical ventilation and administration of manual ventilation for 2 minutes. Superiority of multiple dose over single dose Curosurf for treating RDS was shown.[3]

Of the currently available surfactants, Exosurf is synthetic, and Infasurf, Survanta, and Curosurf are animal-derived (pig lung and cow lung respectively). All are administered in the neonatal period through the endotracheal tube while the infant is receiving mechanical ventilation.

The Study

In 2000, Discovery Labs, a private U.S. drug company, proposed a phase 3 study to demonstrate the efficacy of a new synthetic surfactant called Surfaxin for the treatment of RDS in premature infants. The drug company deliberated with the Food and Drug Administration about an acceptable study design. Although a superiority trial designed to demonstrate the superiority of Surfaxin to Exosurf might have been accepted by the FDA as evidence of Surfaxin's effectiveness, the sponsor did not think it could succeed with such a trial. Based on its experience with previous surfactant studies, the FDA concluded that a noninferiority trial of Surfaxin against Survanta could not yield data that would support the approval of Surfaxin. Despite the clear overall evidence of the effectiveness of surfactants, data on the performance of various clinical measures used in effectiveness studies of each individual surfactant has been inconsistent in studies of the prevention and treatment of RDS. This made it very difficult to identify a credible "noninferiority margin"[4] for surfactant drugs in a comparison trials with other surfactants.

After some deliberation, a multicenter, double-blinded, randomized, two-arm, placebo-controlled trial was proposed to be conducted in Bolivia, and three other Latin American countries. The study population was to be 650 premature infants with RDS. The hospitals chosen for participation in the study generally did not have surfactant available for the treatment of RDS. The sponsor proposed to provide endotracheal tubes, ventilators, and antibiotics for all study participants. The proposal also included sending a team of American neonatologists to supervise the study and help train local health care personnel.

In participating research centers, parents of infants showing symptoms of RDS would be asked to give consent for their infants to participate in the study. With consent, a health care provider would intubate the infants with an endotracheal tube, and either give air suffused with Surfaxin or air without any drug. Endpoints for the proposed study were all-cause mortality by day 28, and mortality due to RDS.

The sponsor planned to set up a data safety and monitoring board (DSMB), as well as a steering committee comprising host-country members to ensure that the trial followed appropriate safety standards.

The principal target market for the drug was the United States and Europe, and the sponsor had no specific plans for marketing Surfaxin in Latin America. However, the

sponsor engaged in some preliminary discussions with the participating hospitals about making Surfaxin available to them at reduced cost if it proved to be efficacious in the trial. No firm agreement was reached in these negotiations.

The Ethical Issues

Surfactants have been used for more than a decade in the treatment of respiratory distress syndrome in infants. Placebo-controlled surfactant trials for premature infants with RDS would currently be considered unethical in the United States and other developed countries because surfactant treatment is widely available and known to improve survival compared to mechanical ventilation alone; a placebo-controlled trial would require withholding life saving treatment that is available to those who can afford it.

Even though financial constraints prevented the Bolivian hospitals from routinely providing surfactant treatment for RDS, the hospitals were of sufficient quality to support and run the ICU facilities promised by the sponsor in return for participation. In the study, although half the infants with RDS would not receive surfactant, they would not be denied a treatment that they otherwise would have received because of economic limits. The ventilator support that both the Surfaxin and "placebo" patients would receive in the proposed study was known to improve survival more effectively than treatments generally available to both groups prior to the initiation of the study. Although offering a higher standard of care than many Bolivian infants would have received, the level of care provided in the control arm—ventilation without a surfactant—would most likely not have been permitted in the United States and other developed countries.

Were the researchers in the Surfaxin trial obligated to use the same surfactant therapies in the control group in Bolivia that would have been required in any developed country? Was it ethical to provide medical care that although better than what the patients normally received was not better than the worldwide best standard of care? Did this study violate the Declaration of Helsinki, which states:

> The benefits, risks, burdens and effectiveness of a new method should be tested against those of the best current prophylactic, diagnostic, and therapeutic methods. This does not exclude the use of placebo, or no treatment, in studies where no proven prophylactic, diagnostic or therapeutic method exists.[5]

If the study was ultimately approved, what information should the Bolivian parents receive? Should they be informed that although this study did not include them, several other surfactants were available for those who could afford them?

NOTES

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Commentary 9.1: Benefit to Trial Participants or Benefit to the Community? How Far Should the Surfaxin Trial Investigators' and Sponsors' Obligations Extend?

Robert J. Temple

The Surfaxin case presents a perfect example of the problem of deciding what constitutes "available" therapy for a population in a trial involving a serious disease. Despite some degree of discussion following the 2000 revision of the Declaration of Helsinki, it is widely accepted,[1–4] and clearly stated in guideline E10 of the International Conference on Harmonization (ICH), Choice of Control Group and Related Issues in Clinical Trials,[2] that patients can be invited to participate in a placebo-controlled trial, even if there is existing available effective treatment, if they will not be harmed that is suffer death, irreversible morbidity, or perhaps very severe discomfort, by the delay or denial of the treatment. In contrast, and not at all debated, patients cannot be randomized to a placebo treatment, when available therapy for that patient population, given as it would be used in the study, is known to prevent death or irreversible morbidity.[1,2]

The ICH E–10 guideline does not consider, however, what "available therapy" means in a clinical-trial context in a country in which limited economic resources means that there will be limited medical services. Other documents have considered this question, but not always persuasively, often using the evocative language of social justice at the expense of rational consideration of the real interests of potential participants in the trial.

The National Bioethics Advisory Committee (NBAC),[5] for example, considered two possible conclusions about what patients in a trial were entitled to: (1) best local therapy or (2) best global therapy. Without a great deal of explanation, they simply chose (2), arguing that this is most compatible with established ethical principles, notably beneficence. They acknowledged an exception, however, where it was critical to the country's interest to study a treatment that might not be as good as the best available treatment, so that an active control trial would be uninformative. In that case, patients could be randomized to the new treatment or placebo. The trials in Asia and Africa of low-dose AZT for preventing HIV transmission to neonates illustrate this case; they have been considered ethically acceptable by most[6–8]

but not all[9] observers, and recent CIOMS guidelines[8] leave ethical room for such trials.

For cases in which the country itself did not need the data for its own public-health purposes, NBAC felt that best global treatment had to be given. Indeed, it actually described the Surfaxin case, concluding that a placebo-controlled trial of a new surfactant could not be performed anywhere, even in countries that do not use surfactants because they cannot afford them, under the rules they were recommending in the report. If that view prevails, and if active-control noninferiority trials would not be informative, then a new surfactant could not be developed unless it was superior to existing surfactants. A key problem is that noninferiority surfactant trials cannot provide evidence of effectiveness because despite the fact that surfactants are known overall to be effective, they do not regularly show superiority over placebo on any given endpoint in a research study. A noninferiority study would therefore lack assay sensitivity, that is, a known ability to distinguish an effective treatment from a less effective or ineffective treatment, and could therefore not provide persuasive evidence of effectiveness from any trial.

The U.S. Food and Drug Administration (FDA) regulations recognize this problem,[10] and make clear that for a positive control noninferiority study to be informative, there needs to be evidence that the trial has the ability to distinguish active treatment from placebo, or from another similarly inactive treatment. But there is a conundrum. Everyone accepts that surfactants have favorable effects on outcome, yet less than half of the placebo-controlled trials conducted have shown a significant effect on mortality and about half have shown significant effects on other major endpoints. The critical question in a noninferiority trial is whether one can define a noninferiority margin, that is, a degree of superiority of the control drug over the test drug that, if ruled out statistically, will show that the new drug has some effect. That noninferiority margin cannot be larger than the effect the control drug is known to have in the noninferiority study. (It would usually be smaller, because in a serious illness, one would want to preserve more than "some" of the control effect.) This "known" effect will not be measured because there is no placebo group. It must be deduced from the prior experience comparing the control drug with placebo. If the control is regularly superior to placebo by a defined amount, that amount can be used to identify the noninferiority margin, that is, the degree of inferiority of the new agent that must be ruled out. It goes without saying that a surfactant is a drug whose efficacy needs to be established with certainty. As a result, the determination of a noninferiority margin for some specific study endpoint is a critical obligation of anyone contemplating an active control noninferiority design.[1–3]

It should be noted that even if someone believed that a noninferiority study could be defined for the surfactant, it is important to a developed country to consider the situation where the active control trial would not be informative. Whatever one thinks of the surfactant case, there will surely be cases in which a noninferiority trial would not be credible for the reasons described above. Finally, the reason an active-control superiority trial would not be the answer here is not the large study size needed. Even a large study would not lead to an interpretable noninferiority study. A showing of superiority, however, would certainly be evidence of effectiveness and the need for a large sample size to show this should not stand in the way of such a study.

It is also important to know that were an active-control trial considered interpretable, it almost surely would be conducted in the United States or another developed country. Given the decreased assurance of the applicability of results of a Latin American trial to the U.S. population there is reason to believe an active control trial would not be done in Bolivia. Therefore, under these circumstances, there would be no trial of any kind of a surfactant in Latin America. Consequently, babies born with RDS in Bolivia would not have received either ventilator support or surfactant. Forcing an active control study might have resulted in more than the 17 deaths from RDS in Bolivia that the advocates of an active-control trial claim a placebo-controlled design would produce.

There is no question that conducting a placebo-controlled trial that denies trial subjects effective therapy widely used in other countries, when the beneficiary of the trial is a developed nation and is not the country where the trial is to be conducted, is unsettling. Nonetheless, it is worth asking the basis for insisting that people in a clinical study are entitled to treatment not available to others in their own country and worth exploring the full consequences of not permitting such a trial. There are at least two aspects of this question that need to be explored.

People in the Trial Versus the Community as a Whole

One discomfort expressed about trials in developing countries relates to whether the trial serves the needs of the community where the study takes place or serves only the needs of a commercial sponsor. Indeed, the 2000 Declaration of Helsinki (paragraph 19) and guideline 10 of the 2002 CIOMS guideline[8] state that any trial in a developing country must in some way serve the needs of that country. Although the sponsor of the Surfaxin trial will make the drug available to the participating community at reduced cost, this will not affect Bolivia as a whole, and the purpose of the trial is primarily to market the drug in developed countries.

The critical question, however, is whether a trial must indeed serve the community in which it is conducted or whether it is sufficient to be a desirable trial for the people who participate in it. In other clinical research situations, we appear to act as if the most important ethical consideration is the interest of the people in the trial. For instance, we are not allowed to increase risks to those who participate in research because the results would be more generalizable to other people.

Although it is recognized that individuals can behave altruistically, contributing time and possible discomfort to the cause of advancing scientific knowledge, it is generally agreed that it would not be ethical to put people at real avoidable risk compared to their prior status even for a considerable benefit to the community. No one, for example, thinks it would be reasonable or ethical to study nerve agent antidotes in humans given harmful doses of such agents even though the public benefit might be very great. The FDA promulgated the "animal rule"[12] to allow reliance on animal studies as evidence of effectiveness for such antidotes because it considered human studies "infeasible." In brief, it seems clear that ethical principles demand that the focus of trials must be on the people in them, not the communities from which they are drawn.

One must then ask why, if everyone in a trial is better off because of participation, and no one is denied anything otherwise available to them, the trial is not ethically

acceptable. In the Surfaxin case, all participants would receive ventilator support, a higher level of care than would otherwise be available, a clear and almost surely life-saving benefit for some infants, but only half would randomly receive the surfactant, which would be very likely to provide additional life-saving benefit.

It is hard to see why a rational patient would not prefer study participation to nonparticipation and, indeed, local authorities were enthusiastic about the trial. If the focus is on trial participants, it seems clear that they receive an advantage by participating in the trial. By analogy with the principle that you should not harm patients for the good of the community, failure to help the community is not a reason not to help the people in the trial. It is also very clear what the consequences of failing to do the studies would be. The infant lives that would have been saved by improved care in all patients and treatment with surfactant in 50% of patients will not be saved. Although there can be no doubt that all patients would prefer to receive active treatment, in an active control trial. But as we have seen, if such a trial were thought to be informative, it would be conducted in the United States, not in Latin America, and patients in Bolivia would receive no benefit.

Is the Placebo-Controlled Trial "Exploitative"?

Once again, the answer depends on whether the focus is on study participants or the whole community. Plainly the proposal makes use of the severe wealth and health care inequalities that exist among countries and regions in the world. These differences are distressing, but there is no easy or rapid way to eliminate them. Importantly, the drug company did not create or foster these inequalities. Furthermore, the world makes use of such inequalities in other ways, accepting goods made at the low prices made possible by cheaper labor, with appropriate debate about how much advantage should be taken of this, but little real debate about the overall situation. It thus appears that not all use of inequalities is "exploitative." There is, for example, a real difference between paying people in a developing country to participate in a study of a substance too toxic to be acceptable in the United States, or one that has had no animal studies to assess its toxicity—a risk that could not be imposed on U.S. citizens—and studying a probably useful treatment in a developing country, but not giving an active drug to everyone. In the first case, people may be worse off than they were before the study and would accept this possible deterioration because they are poor. In the second case, they would be accepting a random possibility of gain with no risk of potential worsening of their state.

While paying poor people to risk their health may be exploitative, offering a benefit to all—although some would benefit more than others—does not seem exploitative, even if it makes use of the fact of their poor medical care.

Summary and Conclusions

It is clear that the fact of disparate access to health care is troubling to everyone and there have been discussions of developed countries' responsibilities with respect to

treatment of AIDS, malaria, diarrhea, and many other illnesses that devastate developing countries. The argument that a placebo-controlled surfactant trial is ethical in a country that is not able to provide surfactant treatment for its citizens is in no way related to the question of whether we should be doing more to change the underlying inequality of the situation; it says only that while that situation obtains, a trial that makes everyone better off is ethical.

NOTES

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Commentary 9.2: The Developing World as the "Answer" to the Dreams of Pharmaceutical Companies: The Surfaxin Story

Peter Lurie, Sidney M. Wolfe

A recent trend in biomedical research is to conduct research in developing countries, rather than just in industrialized ones. The number of new foreign investigators in the U.S. Food and Drug Administration's (FDA) database grew from 988 in the

1990–1992 period to 5,380 in the 1996–1998 period.[1] If the result were therapies for or knowledge relevant to developing country scourges such as malaria or onchocerciasis, this would clearly be a step in the right direction, particularly because pharmaceutical companies have essentially turned a blind eye to the needs of developing-country residents with limited purchasing power. But if the result were a series of research studies with little prospect of generating direct benefit to the local communities, both during the trial and after, we would risk a transformation of contemporary research culture into one with strong echoes of colonialism.

In 1997, we criticized a series of 15 planned clinical trials in Africa and Thailand, including 9 conducted or funded by the U.S. government, in which researchers gave HIV-positive pregnant women in the control arms placebos or drugs not proven to be effective, rather than the proven-effective drug AZT.[2] The trials attempted to identify affordable drug regimens for developing countries to prevent the transmission of HIV from mother to infant. We argued that researchers, particularly those running multimillion dollar trials, are obligated to provide the best scientifically proven intervention—independent of the economic status of the volunteers and regardless of where the study is conducted. In the perinatal trials specifically, we argued that, rather than comparing the less-expensive regimens to unproven regimens or placebo, as the 15 trials planned to do, the less-expensive regimens could have been compared to the proven-effective more-expensive regimens. Such an approach was taken in a sixteenth trial,[3] and, despite the absence of a placebo group, its results left little doubt as to the effectiveness of several less-expensive regimens, while providing additional information comparing their efficacy.

While we never disputed that the researchers in the government-funded perinatal trials actually intended to aid people in developing countries (although we rejected their methods), we always understood that the more worrisome prospect was pharmaceutical company–funded studies in developing countries in which lower ethical standards would be adopted in the pursuit of profit. In the proposed placebo-controlled trial of Surfaxin, a synthetic surfactant for the treatment of neonatal Respiratory Distress Syndrome (RDS), we encountered exactly that situation. The primary concern of Discovery Laboratories, the manufacturer of Surfaxin, appears to have been to conduct a trial with its preferred design in Latin America and then to obtain approval in industrialized countries, where they are likely to reap by far their greatest sales. At the time of the proposed study, pharmaceutical sales in Latin America represented a mere 7% of international pharmaceutical sales, compared with 40% in North America and 27% in Europe.[4]

In an unequivocal demonstration of the double standard represented by the proposed research, Discovery Laboratories planned to conduct a study in Europe in which Surfaxin would be compared to an already FDA-approved surfactant drug. As the internal FDA documents on which we based our exposé of this trial correctly stated, "Conduct of a placebo controlled surfactant trial for premature infants with RDS is considered unethical in the USA." These documents were made available to hundreds of FDA employees in conjunction with an internal FDA Scientific Rounds on January 24, 2001, and were subsequently made public by us in a letter to Health and Human Services Secretary Tommy Thompson seeking that the placebo-controlled study not be allowed to proceed. The meeting had the extraordinarily

inappropriate but revealing title "Use of Placebo-Controls in Life Threatening Diseases: Is the Developing World the Answer?"

Clear Evidence That Surfactant Saves Newborn Lives Available at the Time of Study Design

The basic ethical principle of equipoise requires that, among the community of knowledgeable researchers, there be genuine uncertainty as to a study's likely outcome.[5] In the Surfaxin case, the data documenting the efficacy of previously approved surfactants were overwhelming: there were literally dozens of clinical trials, including many with placebo, that together had demonstrated the effectiveness of both synthetic (like Surfaxin) and natural surfactants before the Surfaxin study was proposed. For this reason, surfactant was described in an article in the *New England Journal of Medicine* as long ago as 1993 as "without doubt the most thoroughly studied new therapy in neonatal care" and as "a major advance in neonatal care."[6] The American Academy of Pediatrics also strongly endorsed the use of surfactant for RDS: "Surfactant therapy substantially reduces mortality and respiratory morbidity for this population."[7]

The Cochrane Collaboration had conducted a meta-analysis of six placebo-controlled studies of synthetic surfactant in the treatment of RDS in premature infants and concluded that the use of synthetic surfactant for the treatment of RDS "has been demonstrated to improve clinical outcome."[8] In a section of the review entitled "Implications for research," the reviewer stated unequivocally: "Further placebo controlled trials of synthetic surfactant are no longer warranted." For each of the 7 outcomes evaluated, there was evidence of substantial efficacy and each finding reached statistical significance. For example, surfactant reduced neonatal (28-day) mortality by 34% (relative to a placebo), mortality at one year by 27%, and pneumothorax (collapsed lung) by 43%. These are the benefits that would have been denied the patients in the placebo group in the proposed Surfaxin trial.

Admittedly, analyses of particular outcomes in particular studies at times did not reach statistical significance, but this was strongly related to sample size. The largest study[9–11] had a total of 1,237 patients in the surfactant and placebo arms and 5 out of 7 outcomes showed statistically significant beneficial effects for surfactant. The 5 smaller studies, all smaller than the proposed Surfaxin study, accounted for 22 of the 24 nonstatistically significant findings and produced only 5 positive findings. However, even the statistically nonsignificant small studies estimated the effect size approximately accurately compared to the meta-analysis, indicating that they were underpowered. This is where the FDA has a crucial role to play in reducing the risk of a false-negative result; it can and should assure that any study is adequately powered.

This strong scientific grounding has two consequences: first, it made it very likely that Surfaxin would prove more effective than placebo and, second, it made the withholding of known-effective drugs from any comparison arm all the more unconscionable. The FDA estimated the neonatal mortality rate among premature infants in the potential host countries to be at least 30%. If half of the infant deaths were due to RDS (this was the case in the U.S. in the pre-surfactant era),[12] the provision of

placebo (instead of another surfactant) to the 325 infants in the control group would have resulted in the preventable deaths of 17 infants.

Historical Trends in the Design of Surfactant Clinical Trials

At the time of the Surfaxin controversy, we examined all 5 Cochrane reviews of surfactant efficacy in the treatment of RDS as well as a book chapter published by the Cochrane review author.[13] We also included 3 additional clinical trials[14–16] that could be identified through PubMed.

A total of 42 randomized trials of surfactant for the treatment of RDS had been published; 22 of these (52%) utilized placebos. Between 1985, when the first placebo-controlled trial appeared, and 1990, a total of 15 placebo-controlled (and no active-controlled) trials were published. Between 1991, when the first active-controlled trial was published, and 1995, both active- and placebo-controlled trials were published, though the former predominated (16/19 trials). From 1996 onward, there were a total of 8 active-controlled trials and not a single placebo-controlled trial. Clearly, the trend in surfactant clinical trials for RDS has been toward active-controlled trials. The proposed Surfaxin study would therefore have been a landmark of unethical behavior—a turning to the developing world to conduct studies that the FDA acknowledged could never occur in the United States. In so doing, the study would have turned back the ethical clock by at least 5 years for developing-country studies, while industrialized-country studies (including the European Surfaxin trial) used active controls.

Alternatives to Placebo-Controlled Trials

Neither federal laws nor FDA regulations actually require placebo-controlled trials for drug approval. Rather, the regulations require "adequate and well-controlled studies," and list 5 types of acceptable studies: (1) randomized, placebo-controlled trials; (2) dose-response studies; (3) active-controlled studies; (4) no treatment, concurrent-controlled studies; and (5) historical controls.[17] Indeed, in some divisions of the FDA, active-controlled trials are commonly used as the basis for drug approval. The field of oncology has for years eschewed pure placebo controls in trials of treatments of cancers for which effective therapy exists. Similarly, drugs for the treatment of pelvic inflammatory disease, bacterial pneumonia, and most other bacterial infections would never be tested against a placebo.

In fact, the FDA has accepted active-controlled trials in the past to support approval of a surfactant. In the FDA-approved label for Infasurf (a natural surfactant), the only 2 clinical trials mentioned are active-controlled trials.[18] Both the treatment and prophylaxis indications were supported by trials comparing Infasurf to Exosurf (a synthetic surfactant). The trials were conducted between 1991 and 1993.

Active-controlled trials may be divided into 2 categories: superiority trials (in which the object is to demonstrate that the new therapy is superior to existing therapy) and noninferiority trials (in which the goal is to prove that the new therapy is not inferior to existing therapies by a prespecified amount). In the Surfaxin case,

the FDA raised questions about a noninferiority trial because previous studies were said to have given inconsistent results. However, we have shown above that the results of previous placebo-controlled studies of synthetic surfactant in the treatment of RDS were remarkably consistent. Statistical significance has not generally been a problem for these extremely effective interventions, as long as the study is adequately powered. As noted, the FDA can assure that this occurs. It is noteworthy that the planned study in Europe was a noninferiority trial.

An alternative would be a superiority study, the basis of approval for Infasurf. The FDA documents state that a superiority study in an industrialized country was not considered feasible by the sponsor due to enrollment difficulties and unspecified "ethics." While these "ethical" concerns in industrialized countries, whatever they were, seemed to resonate with the sponsors, providing second-rate treatment to desperately ill infants in developing countries simply because they were poor apparently did not.

According to the FDA documents, "The sponsor has not yet provided justification for why they haven't planned a superiority trial versus Exosurf in *underdeveloped* Latin American countries" (emphasis in original). Even if one accepted (which we do not) that a noninferiority trial was not feasible, one is left wondering why the FDA did not force the company to conduct a superiority trial as Infasurf had been approved on that basis. Perhaps the company was concerned that Surfaxin would prove no more effective and perhaps less effective than another surfactant, a marketing problem for the company. (As the FDA explained in the documents we obtained, "a superiority trial versus an approved therapy presents a clinical efficacy hurdle that the sponsor deems too high for this drug.")

While this attitude may be understandable from a corporate perspective, the FDA is not charged with promoting corporate interests. If an active-controlled trial is the ethical approach from a patient-protection perspective and provides the most useful data (the clinically relevant question is how Surfaxin compares to already-approved surfactants, not whether it is better than nothing), the FDA should have insisted upon such a design. Instead the FDA has been the leading intellectual force behind attacks on the usefulness of active-controlled trials.[19–24]

Another reason to avoid a superiority trial may be the FDA's claim that a superiority study against Exosurf would take longer to conduct for statistical reasons due to larger sample-size requirements. Of course, this is only true if one expects there to be only a small advantage for the new treatment; clearly superior new therapies can be proved superior with studies that are not very different in size from placebo-controlled studies.[25] Every patent-protected day a drug is on the market is a day of increased profit for the company. But with four surfactants already on the U.S. market and the patients at the participating centers in the four Latin American countries currently receiving none of them, even though some of them were approved locally, why is speed a factor for either U.S. or developing-country patients?

Intra-Trial Issues

We do not raise any objection to the use of placebos per se. Placebos are acceptable when no proven therapy exists or when the condition being treated is mild or

self-limited, such as common headache or seasonal allergy. But they are considered inappropriate in industrialized countries when the best available science has identified a treatment that may reduce or prevent serious harm, improve health, or prolong life. A therapy proven to reduce neonatal mortality by 34% in placebo-controlled trials certainly meets that criterion. In order to justify the withholding of effective therapy in a developing country, therefore, the researchers had to rely on an economic argument: because the other surfactants were unavailable to the potential patients in the developing countries due to cost, the researchers were under no obligation to provide them no matter how strong the science supporting them. This has come to be known as the "standard of care argument." This term, borrowed inappropriately from malpractice jurisprudence (in which physicians can be found liable for damages if they fail to provide the "standard of care" offered by others in their communities), seeks to sugarcoat the ethical sleight of hand that is in operation. Referring to the Surfaxin case specifically, the U.S. National Bioethics Advisory Commission rejected such reasoning: "In studies of this kind—involving a disease that is life-threatening and one for which an established, effective treatment is available—a placebo control is not permissible."[26]

London has distinguished between what he terms the de facto and de jure standards of care.[27] The de facto standard is defined as being set by "the actual medical practices of that community." In contrast, the de jure standard is determined by "the judgment of experts in the medical community as to which diagnostic and therapeutic practices have proven most effective against the illness in question." In part because it has a basis in the rigors of science, not the vagaries of the world economic order, we endorse the de jure approach.

The de facto standard of care argument has two important consequences for the Surfaxin trial. First, it essentially lays waste to the bedrock ethical principle of equipoise. Due to the large number of previously positive phase 3 trials of similar products as well as phase 1/2 studies and animal studies of Surfaxin presumably in the company's possession, there is little question that Surfaxin will prove superior to placebo. There is, however, genuine doubt as to whether Surfaxin will be as efficacious as the already approved surfactants. This is the ideal situation for an active-controlled trial.

Second, the de facto standard of care argument endorses the notion that researchers' responsibilities are determined in part by nonclinical factors external to the trial. This is completely inconsistent with the Hippocratic oath in which physicians undertake to "look upon [God's] offspring in the same footing as my own brothers." As physician-scientists, the only reasonable standard for defining an acceptable control arm is scientific. Patients should not be treated inferiorly because of an accident of birth, residence, or global economic conditions. The laudable work of physicians in bringing anti-HIV treatments to poor countries bears witness to researchers' potential as opinion leaders, influencing the quality of health care delivered in the countries in which they are working, rather than relegating themselves to the status of bystanders who exploit adverse economic circumstances to conduct a study designed primarily to benefit corporate interests. As medical historian Rothman has observed, "As soon as [researchers] attempt to take advantage of the

problem, not observers of it. For usually the investigators have the ability to alter the social deprivation of their particular subjects."[28]

The researcher's obligation to provide interventions to their study participants is not one without limits. We do not suggest that tuberculosis researchers who recognize cases of depression among their patients are obligated to treat those patients' depression themselves. For conditions not being studied but encountered during the course of the study, referral for appropriate care is reasonable, wherever the study is conducted. Nor do we suggest that unreasonable infrastructure building be undertaken before a study can commence. As we have stated previously,[2] a study of the treatment of hypertension in the developing world would not require the construction of a coronary care unit in case the patients develop complications of hypertension. However, reasonable expenditures for care related to the condition under study are, in our view, ethically required when the researchers continue to examine the patients prospectively. The Surfaxin researchers could easily provide an active control drug, particularly since they were planning to go to the effort and expense of upgrading intensive care units so that they could conduct their study.

There are often massive economically based differences in the quality of care provided within a country, even within industrialized countries; these are susceptible to exploitation by any researcher brandishing the de facto standard of care argument. Under such circumstances there is no national standard of care at all: there are those who receive scientifically proven care and those who do not. In the countries where the trial would have taken place (Bolivia, Ecuador, Peru, and Mexico were candidates), surfactants were being used in some hospitals, but, according to the FDA documents, "surfactants are completely unavailable to infants at many other hospitals, secondary to rationing or economic limitations." It is in these latter hospitals that the studies were planned. The researchers thus had to tread a narrow line: they had to identify a target population within a country that was (1) poor enough to not be receiving surfactant; (2) not so well off as to have an expectation of receiving the drug; and (3) receiving care in a facility sophisticated enough to be upgraded to study requirements.

By definition, the proposed trial would have required at least a certain level of infrastructure, because both the placebo and Surfaxin patients would have had endotracheal tubes and would probably have been on ventilators. The logistical feasibility of providing Surfaxin (and thus an active control drug) during the study was therefore not in question, since it would simply have been squirted down the endotracheal tube. Such studies have budgets in the hundreds of thousands, if not millions, of dollars. The physician-investigators who conducted the study would clearly have been making the choice not to provide this lifesaving therapy for some patients, even as they had before them infants suffering from a frequently fatal disease. This represents a very fundamental undermining of the doctor-patient relationship.

Post-Trial Issues

A central tenet of research in developing countries is that the subject of the research must be relevant to the host country's needs.[26] While RDS is certainly an important problem in many developing countries, the notion that the lack of surfactant, which

can only be delivered in sophisticated settings, is an important priority in such countries is absurd, particularly after the previous surfactants had been approved and had proved unaffordable in the proposed host countries. In the more likely event that the study produced findings that were beneficial to patients in wealthier countries but the drug was not widely available in the countries in which it was tested, an additional dimension of unethical behavior would have been added.

The investigators claimed that they would provide benefits to the hospital by training neonatologists and providing the drug to those hospitals after the trial. In other words, they were willing to aid these countries in several different ways—just not the most straightforward way, which would have been to treat the control group. Although that would have spared many infants' lives, it would preclude the company from conducting the study the way it wished. This is the very definition of conflict of interest.

Efforts to improve health care infrastructure are hard to oppose; the problem is that the benefits accrue to people outside the trial, while the actual volunteers may not benefit from these infrastructural improvements. In some cases, subjects may actually be denied care as a quid pro quo for others to receive the infrastructural improvements. The Declaration of Helsinki is clear that the researcher's most fundamental ethical responsibility is to his or her patients: "In medical research on human subjects, considerations related to the well-being of the human subject should take precedence over the interests of science and society."[29]

Absent a clear agreement on paper to make the drug available to the general community after the trial (a "prior agreement"[30]), post-trial availability promises may prove empty. Once the trial has been conducted, developing countries have little leverage to insist upon such availability. Prior agreements must specify, to the extent possible, to whom the drug will be made available, at what cost, and for how long. To our knowledge, the offer from Discovery Laboratories included none of these details.

Some may argue that if the company were not permitted to conduct the study with a placebo, it would instead do an active-controlled trial in an industrialized country, denying the developing country the benefits of the research project. In the first place, this would be an acknowledgment that the company never had any interest in the health needs of the developing country, which is, as we noted above, the most basic prerequisite for any developing country research.[26] It would also dispense with the claim, often heard in the defense of these sorts of unethical developing-country studies, that the research was a product of true collaboration between the sponsor and the host country. Obviously, the fact that Discovery had not even decided in which country the research would occur undermines that argument.

We believe that ethical standards have unique value as a statement of the equality of all persons[31] and are therefore themselves important to maintain; they should not be sacrificed to this kind of coercion. In their absence, exploitative studies are sure to proliferate, to the detriment of developing-country health. The long-term health of people in developing countries will be better served by standards that protect all patients in all studies and set a higher standard for acceptable medical care than by accepting occasional exploitative studies that do not provide full benefit to all subjects. (In the Surfaxin case, the threat proved empty; after the placebo-controlled

study was canceled, the company converted, without apparent incident, to an active-controlled trial at 49 sites in the developing world and elsewhere.[32])

Procedural Safeguards Do Not Guarantee Ethical Trial Designs

When challenged, researchers commonly seek to justify research by claiming that participants are protected by informed consent, Institutional Review Boards (IRBs) and Data Safety Monitoring Boards (DSMBs). We agree that all three of these elements should be in place in such trials, but their presence is hardly a guarantee of ethical research. An unethical research study is an unethical research study even with informed consent, IRB approval, and a DSMB.

There is strong evidence of a lack of informed consent in research conducted in developing countries.[33] An adequate informed consent process in a placebo-controlled Surfaxin study would have to make reference, at a minimum, to the 22 placebo-controlled studies collectively showing the known effectiveness of other surfactants in the treatment of RDS in newborns and would have to explain why these drugs were not being provided to the infants in the present study. It would also have to explain that there have been 20 active-controlled trials and that because the study could not be conducted with a placebo in an industrialized country, it was being conducted in a developing one instead. Even so, the desperate parents of these infants are likely to give consent for the trial, for at least they have a 50% chance of receiving the surfactant treatment. No doubt they would be at least as likely to sign up if they knew they had a 100% chance of receiving an active treatment, as previous research has shown.[34]

Approval by an IRB is critical, but even U.S. IRBs have been severely criticized.[35] The situation in developing countries is most likely still worse. Developing-country researchers who responded to a survey conducted on behalf of the National Bioethics Advisory Commission indicated that U.S. IRBs were more likely than developing-country IRBs to indicate that confidentiality protections in the index study were inadequate, to comment on the need for a local language consent form, and to raise concerns about the complexity of the informed consent form.[36] Twenty-five percent of developing-country respondents indicated that their studies were reviewed neither by the Ministry of Health nor by an IRB or its equivalent. In a concrete example, the *Washington Post* has reported that the apparent local IRB approval of a Pfizer-sponsored meningitis study in Nigeria was based on a document back-dated by one year.[37] In the Surfaxin case, specifically, the proposed trial design was rejected by the Bolivian Department of Health "due to the prevailing legal norms in the country and because of ethical and social reasons."[38] Of course, this would not have prevented Discovery Labs from shopping their protocol to other countries.

The FDA documents also note that a DSMB for the study was proposed. These independent committees review the data periodically as the trial progresses and may recommend halting a study if there is evidence that a treatment is harming or benefiting its recipients more than those in the comparison arm. Implicit in the DSMB's task, however, is the acceptance of the basic soundness of the research

design. Early termination of a study, once the company's goals have been met, does little to benefit those who have already received a placebo.

Summary and Conclusions

The ethical obligation of the researcher is to obtain needed scientific information in the manner most protective of the health of his or her study participants. Given the proven, life-saving effectiveness of other surfactants, a placebo-controlled trial could not satisfy this requirement, and an active-controlled trial was mandatory. Contrary to the FDA's assertions, we believe that a noninferiority trial was indeed feasible from a statistical point of view. Even if one hypothetically conceded that this was not so, the manufacturer was still left with an ethical option: a superiority trial, the basis for the approval of a previous surfactant. Clearly, the company was opposed to this option, leaving unresolved the question of why the FDA did not insist upon the ethical design, even though, as the gateway to the world's most lucrative pharmaceutical market, it holds enormous sway over the industry. But, even if one rejected both active-controlled designs, one would still have to resort to the de facto standard of care argument to justify the withholding of effective therapy from poor patients.

The Surfaxin trial is one of the best examples to date of the race to the ethical bottom that the de facto standard of care argument ensures. Unable to conduct a placebo-controlled study in an industrialized country, or even in the wealthier parts of these developing countries, the researchers hit upon the idea of experimenting on the poorest of the poor, even as they proposed an active-controlled trial in Europe. Such behavior might be expected from a profit-driven drug company. However, it has become clear that the FDA played a central role in supporting this study design.[39] The FDA's role is to prevent such unethical behavior, not to give it the agency's stamp of approval.

Postscript

On April 14, 2004, Discovery Laboratories announced that it had filed a New Drug Application seeking FDA approval for Surfaxin for RDS in premature infants, citing the favorable results from two clinical trials.[40] In the European noninferiority study, Surfaxin proved statistically equivalent to Curosurf, another surfactant.[41] Despite the company's protestations, the second trial was redesigned as a superiority study and implemented in 49 centers, including some in developing countries. In a paper presented at a pediatric conference, the company reported that Surfaxin was more efficacious than Exosurf at preventing the development of RDS at 24 hours (39% vs. 47%) and RDS-related death by 14 days (4.7% vs. 9.6%).[32]

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