

From Uncertainty to Evidence in Medicine, One Trial at a Time

Professor Birgit Grund has applied her statistical skills to a major health crisis in today's world: the HIV/AIDS virus. As part of a large, diverse team of researchers, she helped conduct a clinical trial to test when HIV/AIDS patients should begin treatment. The findings have changed the HIV treatment guidelines here in the United States and across the globe.

Associate Professor Birgit Grund recognized the potential of statistics to help solve important problems at a young age while studying mathematics in Germany. After completing her PhD and postdoc in Europe, she came to the United States and joined the faculty here at the University of Minnesota. "I enjoy collaborating with a lot of people," she says, which led her to branch out to apply her statistical knowledge to other areas, specifically the medical field.

In 1999, Grund became involved with a team researching treatments for HIV/AIDS. At the time, effective drugs had been recently discovered. So far, there is no cure for HIV, but with life-long drug treatment the progression to AIDS can be delayed by decades or prevented altogether. Drugs have side effects, however. Many doctors believed a patient should start treatment immediately when diagnosed with HIV, while many others believed that for healthier patients, watchful waiting would be a better option, delaying treatment and treatment's side effects as long as the patient's immune system was still in good shape. "This was an important question that needed to be asked," says Grund, noting how fast medicine moves in today's world.

Working with the Coordinating Center for Biometric Research at the Division of Biostatistics, School of Public Health, Grund participated in the development of a randomized clinical trial to answer this question. This trial, "Strategic Timing of Antiretroviral Treatment" (START), was conducted by the INSIGHT network, an international organization with centers in 32 countries in Africa, Asia, Australia, Europe, North and South America, and Grund routinely works with doctors and statisticians from all around the world. "I am a small part of a big machine," Grund states, emphasizing the importance of collaboration for high-impact research. The organization receives its funding from major health institutions such as the National Institutes of Health (NIH) and national health agencies in Europe and Australia. Pharmaceutical companies donated the medication.

Before the trial could begin, numerous steps had to be taken. Medical professionals and statisticians had to agree on which questions exactly they wanted answered, and how to do this. They had to decide on their primary outcome measure, on the target population, on how long drug treatment could be safely delayed in one of the groups, and what the results would mean for HIV/AIDS treatment. "These issues all are part of developing a clinical trial," Grund pointed out, meaning a much longer and arduous process was to come. "It takes a year or two to design a large trial, it is a major undertaking," Grund says. The experiment involved observing the development of symptoms and side effects within the two treatment groups: those who were assigned at random to begin treatment immediately and those who were assigned to wait. The experiment started in 2009 and was continued for six years before results became publicly available.

As a statistician, Grund primarily worked on the data analysis. The trial was blinded, meaning that researchers and trial participants did not know preliminary results while the trial was still ongoing. Maintaining the confidentiality of interim results in such trials is very important, in order to avoid prejudice from early, still uncertain data. To protect the participants' safety, NIH convened a Data and Safety Monitoring Board (DSMB), an international committee of specialists who met in Washington, DC, once or twice a year to review summaries of the emerging data, discuss the progress, and decide whether the trial should continue, be changed in some way, or stopped. Grund led a small team of statisticians who produced these interim reports. In 2015, the DSMB recommended to unblind the data, because the trial had answered the research question. The trial had shown that it is beneficial to start treatment immediately, rather than wait. This finding had a large impact on the medical community and changed WHO and the United States' treatment guidelines. "It was very satisfying to work with a committed team toward a common goal," Grund states, emphasizing the importance of helping the community, and in this case, on a global scale.

The research findings made the front page of the *New York Times*, a very exciting time for Grund and her colleagues. "The evidence we found is the gold standard," she notes, adding that all of their hard work paid off. The experiment's results were presented at large AIDS conferences and were published in the *New England Journal of Medicine*, inspiring other research in HIV/AIDS and the publishing of numerous secondary papers.

Meanwhile, Grund's role on the team has changed. She is continuing to work with medical investigators to produce papers and plans to continue researching HIV/AIDS. How did she get into this research? "Pure luck, I was at the right place at the right time," she says with a smile across her face.