As a research nurse, I have two patients—the human patient for whom a research study means a new discovery or treatment and the written protocol, which needs to be nurtured and guided and groomed to reach its successful end.

I had been a research nurse for a long time and pediatric nurse for longer, when a doctor in my department, Endocrinology, asked if I could help her on a new clinical trials for a treatment in patients with Prader-Willi Syndrome. This was for a new treatment for the hyperphagia that is the hallmark of PWS and leads to obesity and its many health related problems. I was flattered to be asked and excited to be a part of this cutting edge research. I was prepared for a routine clinical trial: Setting up the resources we needed to have in place; screening and recruiting patients; educating staff; administering an experimental medication; and teaching families. Little did I know that this study would be a defining moment in my career—calling upon my critical thinking, patient advocacy, and clinical care skills in a way I never imagined.

It all started off routinely enough. Systems were set up, contracts finalized, IRB approval obtained and we began enrolling patients. Our first event occurred on a lovely spring weekend, about 2 months after the study started. One of our patients JG, started showing signs of confusion and then belligerence. She was brought to the ER kicking and biting, extremely confused and agitated. Her poor parents were bewildered by this change in her behavior. While she had always had a difficult personality, she had never been confused. She was medicated and eventually calmed down, but within hours was admitted to the ICU, obtunded and non-responsive. JG's condition frightened her parents and perplexed the medical team, who assumed that this was being caused by the study drug and contacted the PI to ask that the study be unblinded. Both the PI and I felt that this probably qualified as one of those "serious situations" described in the consent form where the patient could become unblinded, as we were both concerned not that the drug was causing this reaction, but that if it was not, that this new baseline for JG was not a good thing. Over the next few days, JG woke up and though still quarrelsome, began to return to her previous baseline. The PI and I, however, were locked in a philosophical battle with the study sponsor who did not want to unblind the patient, but rather wanted her to be worked up as she would for any change in behavior. We explained our initial concerns, as we advocated for JG and her family and the importance of knowing if this was JG's new personality. The family was understandably angry and confused themselves by the sponsor reticence and I was place in an uncomfortable position of trying to defend a decision with which I did not agree. The inpatient team simply began attributing the incident to the study drug in their notes. In addition, I did not know the family well before they started the trial, and though I had grown to know JG and her dad (who was her legal guardian and accompanied her to clinic visits), I had never met her mother. She knew the PI, who had provided clinical care to JG for several years, but immediately assumed that I worked for the sponsor and that what I was doing benefitted them and not JG. I quickly set about correcting that misinterpretation, that I was here to advocate for JG and what was the safest best thing for her. At the same time, as the nurse for the protocol, I understood what the sponsor was trying to say. This patient should have a thorough

workup for whatever the cause of her confusion and knowing the treatment assignment, which had since been stopped, would not make a difference. As time went on and it became clear that JG was going to recover, knowing the treatment took on less importance. She did return to her baseline, but never resumed blinded treatment. The PI and I had many conversations with her family about her options. While I participated in these discussions and offered support and information, I also recognized that this difficult situation fell squarely in the realm of what the PI should be doing and was not something I was responsible for. JG's family decided to continue to have study related testing performed without resuming blinded treatment. At the end of the randomized period, participants could opt to go on unblinded study treatment, and JG and her family opted to do that. Five months after her adverse event, JG began on open label treatment with the experimental product.

Three days after JG began the open label treatment arm of the study, a patient on the same study, at another site, died from a pulmonary embolism. Deep vein thrombosis (DVT) had been previously reported with this drug, but no patients had died. The study was put on an immediate clinical hold by the FDA. After reading the reports from the sponsor, I made the decision that, at least to me, the most important "patient" here were the human ones, and from this point forward, advocating for their safety became my only focus for this study. Fortunately, the study sponsor felt the same way. After a lengthy clinical hold, during which the participants were monitored and tested for signs of emboli, the sponsor decided to stop any further research into the drug and ended the clinical trial.

Because we had been conducting this study in our Clinical and Translational Study Unit (CTSU), I had been working closely with the nurses there in the care of these study participants. Many of them came to monthly meetings of our clinical research group, which met once a month to discuss issues of interest to research nurses in the hospital; because were such a small group and often had no peers inside our respective departments, these meetings provided an excellent forum to share our experiences. The issue of unblinding this study had been one I had been trying to work through and I was continuing to struggle with the ethical dilemma of what in the best interest of the study participants. Research is fraught with ethical issues and so I decided to present this topic to this group for discussion. I developed a brief powerpoint presentation and presented this to the group; a lively and interesting discussion followed. Many had not thought of this issue before; others knew that such situations were possible in their own studies, but had never faced the topic before. While my experience was helpful to others, I also enjoyed hearing the thoughts of others—dilemmas are a double edged sword after all—and incorporating them into the care of my study patients.

As we informed the families of the situation, I was very surprised to learn that many families were willing to risk this very serious side effect to continue a treatment many of them felt had been very helpful. Even JG's family, who witnessed this very serious side effect, wanted to try again. This brought up concerns of therapeutic misconception. Although when consenting and throughout the studies, I always remind families that the purpose of the trial is to see that the drug is effective, it is clear that it is easy for their hopes for success to become reality to them. Our experience with the medical staff showed that this misconception is not limited to families. This did bring home that the consenting process and education of family and staff is an ongoing process throughout the study. I was also able to arrange a talk for our research nurse group on therapeutic misconception.

When I first became a nurse. I worked on an infant toddler floor and cared for many Cystic Fibrosis patients. While I had advanced easily from novice to competent in my clinical skills, I was completely intimidated by this patient population, or should I say the families of this patient population who had been living with this disorder for many more years than I had been a nurse. I tended to shy away from these patients and let my more confident colleagues take over. I had thought these were the most knowledgeable protective parents I had ever met until I started seeing PWS patients. This is singly the most devoted group of parents I have ever met. As an entire group, their depth of knowledge about this condition was astounding and the care they provided their children was something to behold. But as I began to care for these patients, I knew that something in me had changed. Even though I was not as up to date on the care of these patients as their parents were, I now had the critical thinking skills and confidence that I had lacked before. I was able to work together with these families to provide the best care possible, even as the going got tougher and tougher. I was able to advocate for them and for the protocol, and educate the families, sponsor, and my fellow research nurses. Even though the road was rocky, this study brought out the best in what I had to offer both of my patients—the humans and the paper.