

Food and Drug Administration
Center for Devices and Radiological Health
Office of Compliance
Division of Bioresearch Monitoring
Program Enforcement Branch II (HFZ-312)
2098 Gaither Road
Rockville, MD 20850

Attention: Mr. G. Levering Keely, BSN, MPA, Community Safety Officer

Dear Mr. Keely:

I am responding to a warning letter that was generated as a result of a recent inspection of our clinical site. Mr. Allen Hall, an investigator from the FDA's Los Angeles District Office, conducted the inspection at Childrens Hospital Los Angeles from November 5 through 7, 2002. The inspection report revealed violations of requirements of Title 21, Code of Federal Regulations (21 CFR), Part 50-Protection of Human Subjects and Part 812- Investigational Device Exemptions.

We have taken numerous steps to correct these violations and to prevent the recurrence of similar violations in current or future studies. We did an extensive reorganization of the [REDACTED] study to ensure it meets all FDA standards.

With regards to the first violation, "Failure to document the informed consent by use of a written consent form approved by the IRB and signed and dated by the subject or the subject's legally authorized representative at the time of consent. 21 CFR 50.27(a); 812.100; and 812.140(a)(3)(I)", we have revised the SOP for the Informed Consent Process.

Upon notifying the IRB at Childrens Hospital we had not obtained proper informed consent, we discovered that the "system" we had in place was inadequate. While the mistake was purely inadvertent, it was extremely serious, and thus has been addressed with the utmost importance and diligence. We revised the informed consent process to take place once a subject is identified as a candidate for the procedure. Earlier execution and filing of the consent document will ensure its completion, prior to performing surgery. Previously, consent was often obtained on the day prior to, or the actual day of the procedure. There was an incorrect misconception consent needed to be signed as close to the surgery as possible. This has since been clarified. Additionally, the previous system depended on individuals not directly involved in the [REDACTED] study. These individuals had multiple other jobs and concerns on their minds. The current protocol places responsibility strictly within the [REDACTED] team and myself.

Once the study team reaches a consensus to invite participation, the patient and family will be invited to receive specific information about the procedure. They will be informed that this is a research procedure using an investigational device, potential benefits, potential risks, available alternatives, and that participation in this study is voluntary. A copy of the informed consent will be provided to the family to take home and review privately. A return appointment will be arranged with the pediatric pulmonologist in order for the family to ask further questions. At this follow-up appointment, the subject may execute the assent (if applicable) and the parents may execute the informed consent, as well as the Experimental Subjects Bill of Rights (as required by California law). The pulmonologist will sign, as investigator, and a

witness will attest to the voluntary nature of the consent. Copies of signed consents will be provided to the family and placed in the study file by the Project Coordinator. The original consent will be forwarded to the medical record. Previously, had the proper copies been made and distributed appropriately, the misplaced original could have at least been documented. As a final safeguard, the study file will be checked on the pre-op day to verify a proper-signed consent form.

Since the time of the violation the [REDACTED] team and myself have participated in educational conferences relating to informed consent. We have participated in sessions that focused on the background, legal requirements, and practical elements of obtaining research informed consent from parents of subjects, and assent from child subjects.

The FDA was also concerned that information was provided to study subjects or representatives in language understandable to the subject or the representative. 21 CFR 50.20. We currently have a translated short form available for those subjects or representatives who do not speak English and require translation. In addition, we will utilize translation staff if necessary. This service is available via the Cultural and Language Specialists Office. These steps will ensure that informed consent will be adequately provided.

The second violation, "Failure to ensure that the investigation is conducted according to the signed agreement with the sponsor and the investigational plan, 21 CFR 812.100, and failure to maintain accurate records of each subject's case history and exposure to the study device, including supporting data and medical records, 21 CFR 812.140(a)(3) has also since been remedied since the site inspection.

As the clinical investigator, I ensure that the investigation will be conducted in accordance with applicable FDA regulations. I recognize my responsibilities and in the future, if I feel adequate resources are not available, I will refuse to proceed with the study until those resources are made available. Since this violation, we hired a study coordinator to manage the [REDACTED] study. The coordinator will monitor the completion and submission of all case report forms (CRFs) to facilitate completion in a timely manner for all subjects. The coordinator sees that all procedures are completed and properly documented. All procedures and documentation are now centralized through the Division of Orthopedic Surgery, as opposed to having multiple divisions involved. This allows the study coordinator and myself to monitor procedures and paperwork more closely, to ensure timely and complete forms. I have made it clear to all parties involved that these resources are critical to the future of this study and our site's credibility. I appreciate your assistance and allowing us the opportunity to address these violations.

Sincerely yours,

David L. Skaggs, M.D.

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