

consent was executed by each of the subjects enrolled into the *Study* prior to their participation in the study. Examples of this failure include but are not limited to the following:

- Subjects _____ and _____ were screened for the _____ study before signing the informed consent form (ICF). During the inspection, Ms. Christine M. Ponce, Clinical Research Coordinator, stated that this practice was discontinued after the monitor explained screening of subjects prior to signing the consent form was not permitted.

In your response, you state that the subjects completed patient self-assessment forms for disability and pain during routine office visits prior to signing the _____, however, the results of their evaluations were not shared with the study sponsor until each patient had gone through the detailed informed consent process and had agreed to participate in the study. You state that at no point during the process were any subjects' rights violated nor were the physician/patient relationship affected, and no patients were enrolled in the clinical trial prior to signing the informed consent document. Your response is inadequate as it does not indicate what corrective measures you plan to take to prevent this violation from reoccurring. Please submit the corrective actions you have taken or plan to take to prevent this violation from occurring in future studies.

- On _____ subject _____ signed a consent form for the _____ study rather than the _____ study.

In your response, you state that subject _____ signed the correct consent form for Compassionate Use on _____ that the form was approved by St. Anthony's IRB on May 12, 2005, and that there was an error _____ ("Compassionate Use") in the footer of the document submitted to the IRB. You state this was an administrative error that was overlooked by your staff as well as the IRB. You also state that, in the future, you will ensure that all ICFs are carefully reviewed for accuracy before submission to the IRB for approval.

Your response to this violation suggests that you believe that subject _____ signed the proper, IRB-approved informed consent for Compassionate Use under the _____ study and that the only error was in the footer of that document, not in its substance. Examination of the specific form signed by subject _____ on _____ does not support your explanation. In addition to the footer, the referenced informed consent document's study title indicates treatment in the _____. The substance of the informed consent document goes on to state that the study involves the _____ discusses treatment of _____ and indicates that the surgery is _____

to be performed through the nearby organs with potential risks/injuries to not consistent with the study in which this subject was enrolled and raises the question of how this form could have been read by, reviewed, and discussed with the subject without this problem being discovered. This information is

As your response does not acknowledge the factual underpinnings of this violation, it is inadequate. Assuring the accuracy of all ICFs prior to their submission to the IRB for approval is a necessary but separate requirement from assuring that subjects are provided with and sign the correct, IRB-approved consent form applicable to the study in which they are to be enrolled. Please submit the corrective actions you have taken or plan to take to prevent this violation from occurring in future studies.

Failure to ensure an investigation is conducted in accordance with the signed agreement, the investigational plan, and applicable FDA regulations and any conditions of approval imposed by FDA or the reviewing IRB [21 CFR 812.100 and 21 CFR 812.110(b)]

As a clinical investigator it is your responsibility to conduct the clinical investigation in accordance with the signed investigator agreement, investigational plan, and applicable FDA regulations. You failed to adhere to the above-stated regulations. Examples of this failure include but are not limited to the following:

- Two subjects enrolled in the study did not meet the study's inclusion criteria. Specifically:

The inclusion criteria required the subject to be between the ages of and years old as well as have a score greater than or equal to Subject was years old and had an score of hence the subject did not meet the inclusion criteria. In addition, on October 25, 2004, the sponsor requested FDA approval for compassionate use for this subject. The letter indicated that informed consent had been obtained and that the clinical investigator agreed to obtain an independent assessment from an uninvolved physician. However, this surgery had already occurred on prior to the request made to the FDA for compassionate use, and without obtaining the patient-specific informed consent or independent physician assessment required by FDA as conditions for Compassionate Use.

In your response, you state that this subject was erroneously enrolled in the study despite the protocol violations of age and score. This protocol deviation was identified by the sponsor during monitoring, and was reported to the IRB in annual reports as well as FDA in annual study progress reports in the PMA. You state that

the importance of a thorough review of the patient's medical history to ensure that all patients seeking to enroll in a clinical trial meet all of the inclusion/exclusion criteria have been reiterated with study personnel. Your response is inadequate as it does not indicate what specific corrective measures you plan to take to prevent enrollment of patients not meeting protocol requirements from reoccurring. Please submit the corrective actions you have taken or plan to take to prevent this violation from occurring in future studies. In addition, your response addressed other examples of subjects being enrolled under Compassionate Use without meeting the FDA-prescribed conditions by stating that the FDA guidelines have been reviewed with staff and that you will ensure that these guidelines are strictly adhered to in the future. This response is inadequate. Delegation of specific study tasks to other personnel does not relieve you of responsibility for ensuring that the rights, safety, and welfare of the subjects participating in the study are protected. Please provide us with details of the specific training and/or procedures that you have put in place to ensure that subjects are properly enrolled.

Subject had an score of which does not meet the inclusion criteria. We also note discrepancies between dates and data entered on the Self-Assessment form and Enrollment Checklist, including cross-outs and date/data changes that make it difficult to determine what the entry of record should be and when the data was actually entered. However, at the date of enrollment, the information entered on the forms indicates that the subject was not eligible for enrollment.

In your response, you state that this subject had a pre-enrollment score of and that the study coordinator initially scored the questionnaire incorrectly and recorded the score as on the enrollment checklist. You state that the questionnaire was subsequently reviewed and determined to be incorrectly scored, with the actual score being which exceeds the minimum score necessary to meet the inclusion criteria.

We note that neither your response nor the records available clearly indicates that the scoring error was discovered and corrected prior to enrollment, suggesting that the subject was enrolled without a contemporaneous basis for establishing eligibility. In addition to the requirement to conduct the investigation in accordance with the protocol, your responsibilities as an investigator include requirements for maintaining accurate, complete and current records (21 CFR 812.140(a)). We caution you that unexplained changes in data entries may lead to questions about data reliability. Your response is inadequate in that it does not indicate what corrective measures you plan to take to prevent this violation from reoccurring. Please submit the corrective actions you have taken or plan to take to prevent this violation from occurring in future studies.

- Adverse Events (AE) were not reported for eleven of the subjects within the ten working days required by the protocol. Examples include, but are not limited to the following:
 1. Subject _____ experienced _____ at the _____ on _____ and it was reported on November 17, 2005.
 2. Subject _____ experienced _____ on _____ and it was reported on January 25, 2007.
 3. Subject _____ experienced _____ on _____ which was not reported until January 23, 2007. The following AE's for this subject were not reported as required by protocol: severe unremitting _____

In your response, you state that the ten-day reporting requirement as outlined in the clinical protocol was intended to apply to Unanticipated Adverse Device Effects as outlined in 21 CFR 812.150(a)(1). The AEs noted were not “unanticipated adverse device effects” and therefore did not need to be reported to the sponsor within ten days. You state these events were reported to both the IRB and the sponsor in the normal course of the study.

The study protocol states that all AEs should be reported to the _____
In particular, AEs should be reported _____
as soon as possible but in no event later than 10 working days after the investigator first learns of the event.

- Required _____ were not taken for the following subjects:
The study protocol requires that _____
_____ be taken at prescribed visits during the course of the study.

In your response, you state that there are instances where all _____ are not taken at a given study time-point due to the discretion of the _____ i.e., _____ may not be performed on patients who undergo _____ because it may not be medically advisable due to potential disruption of the _____ You state you will continue to work closely with the patients and _____ to ensure that the _____ are performed as required. We caution you that protocol-required tests are to be completed and the deviation/failure to complete the tests must be documented. Please submit the corrective actions you have taken or plan to take to prevent this violation from occurring in future studies.

Failure to prepare and submit a complete and accurate report of an unanticipated adverse device effect within 10 working days after first learning of the effect, to the sponsor and the reviewing IRB (21 C.F.R 812.150(a)(1)).

Severe/Serious Adverse Events (SAEs) for seven subjects were not reported to the sponsor and/or IRB within the required timeframes, and some were not reported at all. Examples of your failure include but are not limited to the following:

1. Subject _____ experienced failed _____ resulting in revision of _____ on _____ which was not reported until January 4, 2006. This subject was also referred by you to a clinician for interventional care of _____ resulting in selective level _____ and, an additional request for palliative treatment was made, consisting of _____

Neither of these events was reported as required by regulation.

2. Subject _____ experienced _____ resulting in left-sided _____ and removal of extruded _____ indicated to be an unanticipated, severe adverse event on the CRF, which was not reported until January 23, 2007.

In your response, you state that every attempt was made to ensure that all SAEs were reported in accordance with the study requirements and as part of your ongoing study management, you routinely conduct retrospective reviews to ensure that all AE's have been captured and reported as required; and, that none of the SAEs identified during these reviews involved the investigational device. You further state that all study personnel have been retrained on the IRB and sponsor reporting requirements. Please provide us with details of the specific training that has been provided to the study personnel.

The violations described above are not intended to be an all inclusive list of problems that may exist with your clinical study. It is your responsibility as a clinical investigator to ensure compliance with the Act and applicable regulations.

Within fifteen (15) working days of receiving this letter, please provide written documentation of the additional actions you have taken or will take to correct these violations and prevent the recurrence of similar violations in current or future studies for which you are the clinical investigator. Please submit a corrective action plan that addresses how you plan to prevent these deviations from occurring in future studies, including policies, procedures, and training with expected completion dates that are being developed and implemented to ensure that informed consent is properly obtained and investigations are conducted in accordance with the investigational plan.

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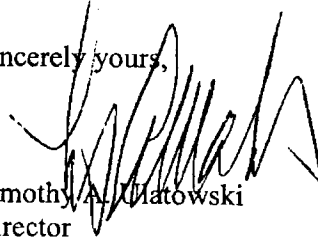
Failure to respond to this letter and take appropriate corrective action could result in the FDA taking regulatory action without further notice to you. In addition, FDA could initiate disqualification proceedings against you in accordance with 21 C.F.R. 812.119.

You will find information to assist you in understanding your responsibilities and planning your corrective actions in the FDA Information Sheets Guidance for Institutional Review Boards and Clinical Investigators, which can be found at <http://www.fda.gov/oc/ohrt/irbs/>. Any submitted corrective action plan must include projected completion dates for each action to be accomplished. Send your response to: Attention: Linda Godfrey, Chief, Food and Drug Administration, Center for Devices and Radiological Health, Office of Compliance, Division of Bioresearch Monitoring, Program Enforcement Branch, HFZ-312, 9200 Corporate Boulevard, Rockville, Maryland 20850.

A copy of this letter has been sent to the Denver District Office, Building 20, Denver Federal Center, P.O. Box 25087, 6th Avenue & Kipling Street, Denver, Colorado 80225. Please send a copy of your response to that office.

If you have any questions, please contact Linda Godfrey by phone at 240-276-0125, or by email at Linda.Godfrey@fda.hhs.gov.

Sincerely yours,



Timothy A. Matowski
Director
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