July 1, 2011

Clinical Research Project

Randomized Crossover Trial Comparing Pump with Subcutaneous Injection Delivery of PTH 1-34 in the Management of Chronic Hypoparathyroidism

Principal Investigator: Karen K. Winer, MD, NICHD, NIH

Associate Investigators: Karen Dowdy, RN; Michaele Smith, MD; Joe Shrader, RM

NICHD protocol: 08-CH-0203

NCT00743782

Investigational Drug Name: Synthetic Human Parathyroid Hormone 1-34

IND Number: 37923

IND Holder: Karen K. Winer, M.D.

Drug produced by the NIH Clinical Center Pharmaceutical Development Section (PDS Chief: Dr. George J. Grimes); Bulk powder supplied by Bachem, CA and the finished injectable drug products formulated by PDS.

IRB approval August 2008, completed December 2013

Clinical Trial Location: Clinical Center, NIH, Rockville Pike, Bethesda MD

Key words: hypoparathyroidism in childhood, hypocalcemia, calcium sensing receptor, autoimmune polyendocrine syndrome type 1 (APS-1), omnipod pump

CLINICAL RESEARCH PROJECT

Date: July 1, 2011

To: Gilman Grave, M.D., Chair, IRB, NICHD

Through: Forbes Porter, M.D. PhD, Clinical Director, NICHD

From: Karen Winer, M.D., Principal Investigator

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Precis

Prior studies (92-CH-0011) have been important in establishing synthetic human parathyroid hormone 1-34 (PTH) as a beneficial treatment for hypoparathyroidism, superior to conventional therapy with calcitriol and calcium supplements. The simultaneous normalization of serum and urine calcium, phosphorus, magnesium and markers of bone turnover remains the main goal of this hormone replacement therapy. Abnormalities in mineral homeostasis, characteristic of hypoparathyrodism, are not remedied with conventional therapy and remain problematic with both once and twice daily PTH injection therapy. Further refinement and physiologic control of calcium metabolism in PTH replacement therapy of hypoparathyroidism are needed. We will be conducting a short-term, inpatient-outpatient study of 24 subjects in a randomized crossover study comparing twice-daily subcutaneous injections vs. PTH pump therapy. We hypothesize that PTH pump therapy will provide smoother metabolic control of serum mineral levels and normalization of urine mineral excretion compared to a twice-daily regimen. The protocol design includes three inpatient admissions: baseline, 3 months, and 6 months. There will be two study arms (PTH delivery by pump vs twice daily subcutaneous injections; each arm divided into an inpatient and an outpatient phase. Subjects will be randomized to either pump therapy or to twice daily injections at the beginning of the study and will cross over to the alternate PTH delivery system (injections vs. pump) at the conclusion of the initial 3-month (13 weeks) treatment period. A central goal of the study is to gain experience with the use of PTH pump therapy as an alternative to multiple daily injections and to establish safety and efficacy. Although the pump is widely used in type 1 diabetes for delivery of insulin, this delivery system has never been applied to PTH therapy for hypoparathyroidism. This study will test the ability of the insulin pump (omnipod) to maintain normal mineral levels and to confirm the device does not adversely impact calcemic control or patient compliance. Additionally, the study will demonstrate whether PTH delivered by pump is sufficiently well tolerated to expect adherence will be satisfactory.

PROTOCOL

Background and Scientific Justification

Hypoparathyroidism is a rare condition resulting in abnormalities in mineral metabolism. Hypocalcemia leads to neuromuscular irritability causing tetany, cramping, carpal pedal spasms, and seizures. Conventional therapy with vitamin D analogs increases intestinal calcium absorption, which increases serum calcium levels but does not correct the lack of renal calcium reabsorption that is typical of this disorder. Normalization of serum calcium levels with conventional therapy is often accompanied by abnormally high levels of urine calcium. Chronic hypercalciuria, a frequent consequence of conventional therapy, may lead to nephrocalcinosis, renal insufficiency or failure (1-11). Iatrogenic hypercalciuria, the result of the interplay of therapeutic intervention to normalize serum calcium levels and compromised physiological defenses against rising urine calcium concentrations, is the limiting factor in the management of hypoparathyroidism. The attempt to normalize serum calcium levels causes a vicious cycle of recurrent hypercalciuria which leads to permanent renal damage. This causes significant morbidity in most patients, and eventually leads to renal insufficiency and, in some cases, renal failure. This possibility precludes the maintenance of eucalcemia over a lifetime of hypoparathyroidism and thus full realization of the long-term benefits of adequate calcemic control. Thus, most patients suffer from chronic symptoms associated with hypocalcemia, which is required to avoid renal damage. The Vitamin D analogs remain the only FDA approved and generally available treatment. Chronic hypoparathyroidism is one of the few remaining hormonal insufficiency states for which replacement with the missing hormone is unavailable. PTH injections have enabled, for the first time, simultaneous normalization of serum and urine calcium. Further refinement is possible as serum magnesium and phosphorus and bone turnover markers remain abnormal in many patients. Additionally, there are transient episodes of hyper and hypocalcemia intermittently through the day with both once and twice daily injections. Therefore, twice daily PTH has been shown to improve urine calcium excretion with overall simultaneous normalization of serum calcium, this method of delivery of the drug is not yet entirely physiologic.

PTH replacement therapy in hypoparathyroidism has been studied in three prior clinical trials (92-CH-0011). The initial pilot study of 10 patients (12) demonstrated that PTH maintained both serum and urinary calcium in the normal range over a 24-hour period when given as a daily subcutaneous injection. PTH resulted in a lower urinary calcium level than calcitriol for a given level of serum calcium and maintained serum calcium within the normal range as well or better than calcitriol. Fluctuations of serum calcium within the normal range were produced in response to PTH injections. Subsequently, results of a randomized controlled dose study (13) showed that twice-daily, compared to once daily, PTH provides effective short-term treatment for hypoparathyroidism with a markedly reduced total daily dose, an apparent reduction in bone turnover, and a decreased incidence of bone pain compared to a once-daily regimen. Twice-daily PTH produced higher levels of serum calcium, with fewer fluctuations into the hyper and hypocalcemic range. Markers of bone turnover were elevated above the normal range in response to both treatment regimens, however, twice daily produced significantly lower serum marker levels suggesting that this dose regimen increased bone turnover to a lesser extent than once daily PTH. Furthermore, serum phosphorus levels remain elevated during PTH injection therapy. In the third study, 27 adults with hypoparathyroidism were randomized to either calcitriol or PTH (14). Our findings demonstrate that twice-daily PTH administration maintains serum calcium in the low normal or just below the normal range over a 3-year period with concurrent normalization of urinary calcium excretion. In the PTH treated group, however, serum phosphorus remained elevated and markers of bone turnover (osteocalcin, alkaline phosphatase) were significantly elevated during the three-year study, at levels at least two-fold greater than normal. Despite this increase in bone turnover, there was no change in the BMD as measured with dual energy x-ray absorptiometry (DXA). Thus, it follows that, all other factors being equal, reducing the calcemic fluctuation and eliminating transient episodes of hypercalcemia will also reduce hypercalciuria. Furthermore, it follows from the pathophysiology, that these improvements in the calcemic profile will ultimately be more physiologic for the kidney and bone.

Objectives

The primary objective of this pilot study will be to evaluate the safety, biological activity and pharmacodynamics of PTH 1-34 comparing delivery by twice daily subcutaneous injection vs.an insulin pump. The levels of serum calcium, phosphorus, magnesium, 1,25 OH vitamin D, bone markers, and mineral levels and cyclic AMP in the urine are the key physiologic responses to determine the adequacy of the PTH effect on hypoparathyroidism. We hypothesize that the delivery of PTH via pump therapy will maintain serum calcium in the normal range with minimal or no fluctuations in blood mineral levels. We anticipate that the small increments of PTH released by the pump will result in a normal physiologic pharmacodynamic profile of

serum calcium, magnesium, phosphorus and 1,25 vitamin D, normalize urine calcium and cause mild increases in urinary phosphorus and cAMP with no apparent peaks or troughs throughout the day.

This protocol is being conducted to study PTH delivered via pump vs. twice daily subcutaneous injections. PTH therapy via pump or twice-daily subcutaneous injections will be compared in a randomized crossover study consisting of two 3-month treatment arms.

The specific hypotheses and study endpoints are as follows:
We hypothesize that PTH pump therapy will be better tolerated, more convenient, and the preferred treatment modality. We expect that pump delivery of PTH will provide smoother metabolic control of serum and urine mineral levels compared to twice-daily injections. Our premise is that pump delivery will produce a more physiologic delivery of PTH by reducing brief episodes of hyper- and hypocalcemia throughout the day, will

permit improved calcemic control in the blood and will be more physiologic to the bone and kidney, with normal bone markers and reduced urine calcium.

The primary objective of this pilot study will be to evaluate the safety, efficacy, and pharmacodynamics of PTH1-34 given as twice-daily subcutaneous injection compared to an insulin pump. The levels of serum calcium, phosphorus, magnesium in the blood and urine are the key physiologic responses to determine the adequacy of the PTH effect on hypoparathyroidism. We hypothesize that the delivery of PTH via pump therapy will maintain serum calcium in the normal range with minimal or no fluctuations in blood mineral levels.
We expect that occasional or no episodes of hypo or hypercalcemia will occur during both daily (pre-dose lab testing) or 24 h testing periods. Furthermore, there will be no diminishing effects of the pump's ability to maintain normal mineral homeostasis over the 3-month period.

Secondary objectives are:
Secondary objectives include measuring serum 1,25 OH vitamin D and cyclic AMP in the urine.
Biochemical marker of bone health: markers of bone formation and resorption in the blood and urine.
To determine if PTH therapy provides significant relief to patients with hypoparathyroidism who generally complain of debilitating fatigue, muscle weakness and decreased endurance. Fatigue scale questionnaire, a self measure of impact of fatigue (15) on activity and 6-minute walk-run test, a test of cardiovascular fitness and functional capability , in accordance with the guidelines and methods described and established by the American Thoracic Society (16,17). A biodex test of muscle endurance will also be performed. These tests will be administered in the Rehabilitation Medicine Department. These measures may help determine if PTH provides significant improvement of these symptoms. This section of the protocol will be performed by the Rehab Medicine collaborators.

Study Design/Sample Size: Study including 24 subjects with chronic hypoparathyroidism comparing PTH pump delivery vs twice daily PTH 1-34 injections.

Summary of Protocol
Patients with hypoparathyroidism who meet the inclusion criteria will be admitted to the Clinical Center for an initial inpatient dose-adjustment phase lasting 7-10 days. PTH therapy (via pump) or twice daily subcutaneous injections will be compared in a randomized crossover study consisting of two 3-month treatment arms. Randomization to either twice-daily or pump PTH therapy will take place at the beginning of the first admission. The initial admission will consist of daily urine and blood collections for mineral levels to determine the best dose of PTH. During the pump arm only, toward the end of the initial dose adjustment phase (day7), there will be a 24h test of serial blood collections to further determine if the dose of PTH is adequate. Patients will be discharged and followed on an outpatient basis for 3 months. During this period, weekly serum and urine mineral levels will be measured. After 3 months, patients will be re-admitted to the Clinical Center. At the beginning of this admission, a 24-h serial test will be performed to measure serum and urine minerals, serum vitamin D and urine cyclic AMP levels. The patients will then cross over to the opposite treatment arm and will undergo the identical measures for the second 3-month treatment arm. The third and final admission will last 3-5 days. At the conclusion of the study, patients will be discharged to their local physicians for care of their hypoparathyroidism. Investigational drug preparation and randomization will be carried out by the NIH Clinical Center Pharmaceutical Development Service. At baseline, 3 months, and 6

months, subjects will undergo evaluation in the Rehabilitation Medicine department for evidence of muscle weakness, decreased stamina and fatigue. This is an important part of the study as we hypothesize PTH therapy will provide a substantial improvement.

Inclusion and Exclusion Criteria

Inclusion criteria: This study will include patients of both genders (ages 7-70) with biochemically confirmed chronic hypoparathyroidism of at least one year duration. Twenty-four subjects will be enrolled. We will recruit adults with post-surgical hypoparathyroidism and children with congenital forms of hypoparathyroidism including APS-1 or hypocalcemia due to an activating mutation of the calcium receptor.

Exclusion criteria: Subjects who meet any of the following criteria are not eligible for the study. Presence of significant hepatic or kidney disease. Pregnancy. Patients who are calcium infusion dependent and/or do not respond to calcitriol therapy to maintain normal levels of serum calcium will be excluded. Seizure disorder requiring antiepileptic medications.

Exclusion criteria for biodex muscle testing in the RMD: Subjects with the following conditions will not participate in the biodex testing portion of the protocol: Any pathology of right knee or elbow consisting of, but not limited to, joint instability, pain, or evidence of an active inflammatory or infectious process. Skin in these areas must be intact; there can be no open or healing wound of the right knee or elbow.

Enrollment and Baseline Data Collection

Potential subjects will be evaluated for study eligibility through the evaluation of their medical history, lab data and performance of a physical examination by a study investigator.

Informed consent: Prior to their admission, eligible subjects will be invited to participate in the study, and the study procedures will be initially discussed over the phone. At their first inpatient admission, eligible adult subjects will be given a consent form to read and, after discussion with the investigators, if they agree to participate, the consent form will be signed. The consent will be discussed with each subject at a level they can understand. Written informed consent must be obtained prior to performing any study-specific procedures that are not part of the subject's routine care.

Prior to obtaining protocol consent, screening labs will be obtained on subjects to determine protocol eligibility. The NIH general admission consent form (NIH-1225-1) will serve to obtain the patient's consent to obtaining this laboratory evaluation.

Patient evaluations: There will be three inpatient admissions at baseline, 3 and 6 months in the NIH Clinical Center. Patients with hypoparathyroidism who meet the above criteria will be admitted to the Clinical Center for an initial baseline inpatient evaluation, patients will be randomized to initially receive one of two possible replacement PTH1-34 regimens: (a) given subcutaneously twice daily or (b) pump therapy. PTH therapy will be initiated. and dose-adjustment will proceed to optimize doses and to maintain normal levels of serum calcium, phosphorus and magnesium and to reduce urine calcium levels. After discharge, patients will be followed on an outpatient basis in collaboration with a local physician and lab. Crossover to the other treatment arm occurs at the second inpatient admission.

Rehabilitation Medicine: Patients will be seen in Rehabilitation Medicine at baseline, 3 months, and 6 months. Fatigue scale questionnaire, a self measure of impact of fatigue on activity and 6-minute walk-run test, a test of cardiovascular fitness and functional capability , in accordance with the guidelines and methods described and established by the American Thoracic Society. A biodex test of muscle endurance will also be performed. These tests will be administered in the Rehabilitation Medicine Department.

Nutrition: A dietary consultation will be obtained at each inpatient admission to determine the patient's usual daily calcium intake, and to review standard recommendations for dietary calcium, given the patient's age and body size. Patients will be instructed to maintain approximately the same calcium intake during the inpatient and outpatient phases. Our recommendation for daily intake is 1000-2000 mg of elemental calcium per day. A fixed diet (time and amount of calcium intake) will be provided during the 24-h testing day.

Monitoring of Subjects

Baseline (Admission 1): Admissions will include height, weight, general medical history, urine pregnancy and a physical exam. Additionally, routine hematological evaluation (CBC), hepatic function studies, mineral panel, alkaline phosphatase, thyroid functions, vitamin D, intact PTH. Daily AM fasting blood: acute care and mineral panels, every other day (x 3 collections) blood and urine collections for bone markers: serum osteocalcin, bone specific alkaline phosphatase, 24-hour urine pyridinium crosslinks. Daily 24-hour urine collections will be obtained for measurement of calcium, phosphate, magnesium, and creatinine clearance. Patients will fill out a symptom questionnaire to determine their symptoms related to hyper- or hypocalcaemia. At the 3-month and 6-month time points, the response to therapy will be compared and examined over a 24-h period with every 2 h measures of mineral levels in the serum and every 4 h measures in the urine. Fatigue scale questionnaire (Self measure of impact of fatigue on activity) and 6-minute walk-run test, and a Biodex test for muscle endurance will be administered in the Rehabilitation Medicine Department at baseline, 3, and 6-month time points.

1. The Clinical center admission 1 and 2 will last approximately 10-12 days and include the following:
    - Monitoring of effects of PTH with q12 hr serum calcium levels: Twice daily blood calcium levels may be performed during the initial days of pump therapy monitoring to identify the optimal basal rate. The PI will determine the need for serum calcium levels at this frequency.
    - If a subject reports symptoms of hypocalcemia, the blood calcium will be checked. When the blood calcium is <1.7 mmol/L mg/dL, the subject will receive treatment for hypocalcemia by increasing the dose, providing calcium carbonate (600 mg calcium PO) or with 1 cup of calcium fortified orange juice. Additional calcium measurements will be made as needed until the blood calcium is >1.8 mmol/L
    - Subcutaneous injection or pump teaching
    - Assessment of the baseline pre-PTH measures of fatigue endurance and muscle strength and endurance.
    - Day 7, pump subjects will have repeated serum mineral testing every 2 hours for 24h to further refine dose adjustment. This test will be done at the beginning of the pump arm and will provide more information to determine the dose. If there are patient care issues that indicate that it would be preferable not to perform this test, such as poor intravenous access, the test will not be done.
2. The outpatient phase will last 3 months and include the following:
    - Daily PTH therapy as prescribed by study investigators
    - Weekly monitoring of serum mineral levels
    - Subjects may be asked to obtain more frequent testing if there is any concern with calcemic control
    - Measurement of urine calcium and markers of bone turnover on a monthly basis.
    - Phone calls to each subject on the first outpatient day and then approximately every 3 days (twice a week) for the first 3 weeks and then weekly until the subject's 3–month follow up admission.
    - Occurrence of side effects or adverse events will be solicited during each phone contact and at the 6-month follow-up visit.
3. Second admission to mirror the first admission and will last 10-12 days.

    The second admission will occur 3 months after the first visit at which PTH use was first initiated.
    - Subject will arrive in the NIH CC for admission. Monitoring of serum and urine mineral levels for three days.

- On admission day 4 an intravenous catheter will be inserted for repeated serum calcium phosphorus, magnesium, 1, 25 OH vitamin D measurements. Blood measurements will be made every 2 h and urine collections every 4 h.

4. Third admission will be identical to the second admission and will contain the repeated testing on admission day 4.

- The subject will be given a small supply of PTH (2 weeks, at the identical dose to PTH injection therapy as determined during this study), while he/she awaits his/her first outpatient visit with the primary care physician.

- There will be a phone contact approximately 4 days after discharge to review hypoparathyroid management and to make adjustments. Additional contacts will be made, if necessary, with their local physician.

- Rehabilitation Medicine consult. Patients will fill out a symptom questionnaire to determine their symptoms related to hypo- or hypercalcemia. Rehabilitation consult as described above.

Outpatient blood and urine collections: Each subject will be discharged with clear instructions on medication doses and follow-up procedures for adjusting their medications. Every week for the first month, and then twice monthly, protocol patients will go to a local laboratory near their home for measurement of serum mineral and alkaline phosphatase values. These data will be used to monitor and adjust the PTH dose.

Medications

Treatment with PTH: Subjects will be randomized at the beginning of the first inpatient admission and will remain on this dose schedule until the second admission (3 months later). Synthetic human parathyroid hormone 1-34 will begin on day 3 of the first admission and will be given as a twice daily subcutaneous injection as a divided dose at 0800 h and 2000 h or via a pump. PTH is prepared by the Clinical Center PDS in two vial strengths: 50 mcg/mL and 200 mcg/mL. The initial PTH dose will be 0.5 μg/kg/day for twice daily dosing and 0.2 μg/kg/day for pump therapy. The total daily dose will be adjusted by approximately twenty percent increments for mild hypo- or hypercalcemia. For severe hypocalcemia, the dose will be adjusted by larger increments and calcium supplements may be added. For severe hypercalcemia, the patient will stop the drug for at least one day and then resume treatment at a lower dose. For further details of pump therapy, see appendix 2

Criteria for Withdrawal of Subjects from the Study

Voluntary withdrawal from the protocol is always an option for the research participants. The following conditions will require the withdrawal of a subject from the study:
Pregnancy; new onset illness that requires chronic use of a medication that adversely effects the kidney or bone such as glucocorticoids, significant deterioration in metabolic control on PTH; severe chronic muscle or bone pain or other unexpected new onset chronic medical condition that can not be explained and may be related to PTH therapy such as weight loss. Subjects who develop tumors will be withdrawn from the study.

Protocol Stopping Criteria

(1) Blood mineral levels cannot be maintained in the normal or near normal range. (2) Persistant mistakes by subject in pump use suggesting an inability to understand how to change doses. Protocol withdrawal would be a last resort after repeated training sessions during the Clinical Center admission. (3) Persistant mistakes in drawing up the PTH dose from vial demonstrating an inability to self inject. (4) An episode of severe hyper- or hypocalcemia (requiring medical intervention) that cannot be explained (noncompliance or dose error) and remedied with usual adjustment in dose.

Sample Size Justification: Our power estimates were based on the ability to observe a significant increase in serum levels of each outcome at the 6 h time point, when PTH is known to peak after a subcutaneous injection. Based on our previous data, serum calcium levels exhibited the most variability and thus sample size calculations are based on this variable. Studies investigating the impact of subcutaneous delivery of hPTH 1-34 on serum calcium levels demonstrated an increase in serum calcium from 2.0 +/- 0.05 mmol/L at baseline to 2.3 +/- 0.10 mmol/L at 6 h. With a standard deviation of 0.10 mmol/L, a two-sided significance level of 0.05 a sample size of 8 subjects will provide 93% power to detect an increase in serum calcium of 0.10 mmol/L.

We will initially enroll 8 adults with chronic surgically induced hypoparathyroidism and study them in a randomized controlled study on both BID injections and PTH infusion pump therapy. We will subsequently enroll 16 children with more severe forms of hypoparathyroidism: calcium receptor mutation or autoimmune polyglandular failure.

Human Subjects Protections

Risks and Discomforts: The risks to the subjects are the pain of blood drawing and the risks associated with the bone biopsy as outlined below. Blood drawing by experienced personnel limits the risk of excessive pain, bruising and infection.

(1) Pain associated with daily blood withdrawals and IV insertion.
(2) Urine collections are an inconvenient but important part of the study.
(3) Possible hypocalcemia or hypercalcemia: Participants in this study may experience symptoms of hypocalcemia or hypercalcemia before the proper dose of PTH is established. Patients who develop hypocalcemia will receive oral calcium supplementation until a sufficient dose of PTH is established. Severe hypocalcemia will be treated with intravenous calcium. Mild hypercalcemia will be treated by downward dose adjustment. For severe hypercalcemia, the patient will stop PTH therapy for at least one day and then resume treatment at a lower dose.
(4) Development of resistance to PTH. These patients will show diminishing responsiveness to the therapy and will require increasingly greater doses of PTH to maintain normal serum calcium. Among the patients who develop resistance, many will be able to continue therapy if the resistance is small or partial. Others may develop substantial resistance with unstable serum calcium and phosphate levels. PTH therapy will have to be discontinued in these patients and calcitriol will be reinstituted.
(5) Animal studies with rats with normal parathyroid function given up to seven times physiologic doses of PTH 1-34 daily from the time of weaning, for 18 months duration, demonstrated that some animals developed osteosarcomas. Although this experiment has little relevance to replacement therapy in humans, the remote possibility of bone cancer remains a risk factor.
(6) Subjects may experience muscle soreness or pain during the muscle contraction test that is expected to quickly subside within minutes following the test.
Potential Benefits: Patients will likely receive direct benefit from their participation in the NIH study. They will be treated with the investigational drug PTH, which is not FDA approved for this disorder, but provides superior metabolic control. In addition, they will benefit from care by the principal investigator who is an expert in the care and monitoring of this rare disease.
Confidentiality protection: Several safeguards will be in place to protect the confidentiality of research findings. All data will be stored on computer that is password protected. Hard copies of forms will be identified by ID number only.
Adverse Event Reporting: All unanticipated new onset medical conditions will be reported to the IRB and FDA. Adverse events will be reported to the IRB and the FDA according to approved FDA and NIH guidelines.

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Appendix 1

SERIOUS ADVERSE EVENT REPORT FORM

Definition of a serious adverse event: For the purposes of this form, a serious adverse event is any untoward medical occurrence that results in death, is life-threatening, requires or prolongs hospitalization, causes persistent or significant disability/incapacity, results in congenital anomalies/birth defects, or in the opinion of the investigators represents other significant hazards or potentially serious harm to research subjects or others. A serious adverse event is considered unexpected if it is not described in the Package Insert or in the Investigator's Brochure (for FDA investigational agents), in the protocol, or in the informed consent document.

Please complete the information requested below and forward it to your Institute's IRB, with a copy to your Clinical Director, as soon as possible, but no later than seven (7) days in the case of death or life-threatening serious adverse events or within fifteen (15) days after the occurrence of all other forms of serious adverse events. In addition, continue to follow FDA and the NIH Office of Biotechnology Activities (OBA) reporting requirements if your research involves an IND / IDE or gene transfer.

1. Protocol number:

2. Protocol title:

3. Principal Investigator:
   Institute:
   Office:
   Phone:
   FAX:
   E-mail:

4. Date of serious adverse event:

5. Location of serious adverse event (e.g., at NIH or elsewhere):

6. Was this an unexpected adverse event? Yes [ ] No [ ]

7. Brief description of subject(s) Sex: Age:
(do not include identifiers) Diagnosis:

8. Brief description of the nature of the serious adverse event (attach description separately if more space needed):

9. Category (outcome) of the serious adverse event:

[ ]death [ ] disability / incapacity

[ ]life-threatening [ ] congenital anomaly / birth defect

[ ]hospitalization-initial or prolonged [ ]required intervention to prevent permanent impairment

[ ]other:

10. Relationship of Serious Adverse Event to research:

[ ] 1 = Unrelated (clearly not related to the research)

[ ] 2 = Unlikely (doubtfully related to the research)

[ ] 3 = Possible (may be related to the research)

[ ] 4 = Probable (likely related to the research)

[ ] 5 = Definite (clearly related to the research)

11. Have similar adverse events occurred on this protocol? Yes [ ] No [ ]

If "Yes", how many? ____ Please describe.

12. What steps do you plan to take as a result of the adverse event reported above? Provide documentation to the IRB for review and approval of any of the steps checked below.

[ ] no action required [ ] amend protocol

[ ] amend consent document [ ] inform current subjects

[ ] terminate or suspend protocol

[ ] other (describe)

Signature of Principal Investigator: _____

Date: _____