

**THE EFFICACY OF BOTULINUM TOXIN TYPE A  
IN TREATING PEYRONIE'S DISEASE**

**PROTOCOL #: 04-07-30-02**

Protocol Date: **January 30, 2015**

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KEY WORDS: Botulinum, Peyronie's, injection

IND#: 104,820

FUNDING SOURCE: Grant from Allergan, Inc.

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This clinical research protocol will be conducted in accordance with FDA, ICH and IRB regulations and guidelines.  
The Scott Department of Urology complies fully with the HIPAA guidelines.

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## I. BACKGROUND AND RATIONALE

Over the past several years botulinum toxin type A (BTX-A, BOTOX<sup>®</sup>) has been used in many applications to prevent scar formation. Gassner and Sherris previously found that chemoimmobilization of facial wounds with BTX-A improved wound healing and cosmetic appearance.<sup>1</sup> These clinical findings are supported by a randomized, double-blinded, placebo-controlled study showing a significant improvement in scar appearance in BTX-A treated facial wounds compared to saline injected controls.<sup>2</sup> In addition, we recently published the first article demonstrating that BTX-A is effective in treating urethral strictures, which are caused by scar formation.<sup>3</sup> Finally, Comperat and colleagues demonstrated that BTX-A injections in the bladder leads to less fibrosis. In the study, bladder wall specimens were obtained from cystectomy in 45 patients with neurogenic overactive bladders with and without injection of botulinum toxin A into the detrusor. Bladder wall specimens were evaluated for inflammation, edema, and fibrosis. When comparing specimen from patients who had received botulinum toxin injection to those from patients who had not, there was no difference concerning inflammation and edema. However, patients who had received botulinum toxin injection showed significantly less fibrosis of the bladder wall than those who had not received the toxin injection ( $p < 0.00073$ ).<sup>4</sup>

A major contributor to fibrosis and scar formation is thought to be tension from the underlying muscle contractions acting on the wound edges during healing.<sup>2</sup> BTX-A acts at the neuromuscular junction by blocking vesicle transport of acetylcholine, in essence producing a chemical denervation.<sup>5</sup> By decreasing underlying muscle tension/spasm in healing wounds BTX-A may be a viable option to prevent fibrosis and scar formation.

Penile curvature secondary to scar or plaque formation along the shaft of the penis is known as Peyronie's disease. Significant penile curvatures can result in pain, poor erections, and an inability to engage in sexual intercourse. Peyronie's disease is an acquired disease of the tunica albuginea surrounding the corpora cavernosa of the penis and affects approximately 3% of the male population.<sup>6</sup> The average age of onset of this disease is 57 years old. The etiology of Peyronie's disease remains unknown. However, many believe that traumatic inflammatory changes to the septal fibers of the erect penis from either blunt penile injury or repeated microtrauma associated with sexual activity.

Traditionally, treatments for Peyronie's disease have been limited and often unsuccessful. Oral medical therapies that prevent the scar formation and promote scar breakdown have been ineffective. Many patients with Peyronie's disease will require injection therapy of the penis. Injections of pharmaceutical agents directly into the Peyronie's plaque have been used for over 50 years in the treatment of clinically significant Peyronie's disease. The three most common agents used for injection therapy are verapamil, interferon, and collagenase.<sup>7</sup> Intracellular calcium levels play an important role in the metabolism and synthesis of collagen. Calcium channel blockers such as verapamil increase collagenase activity and decrease collagen secretion, although quite high tissue doses are needed for this. Interferons are low molecular weight proteins involved in the normal function of the body's immune system. They are known to inhibit the proliferation of myofibroblasts, decrease collagen production, and increase the activity of collagenase. Finally, collagenase is a purified bacterial enzyme that attacks and

breaks down collagen. It has been used clinically to treat severe burns and lumbar disk disease. All three of the agents have been shown to result in mild to moderate improvement in penile curvature when compared to placebo.<sup>7</sup>

There are two phases of Peyronie's disease: the active phase and the quiescent phase. The active phase usually occurs during the first 12 months of the disease and is associated with constant changing of the plaque and penile pain. Surgery is contraindicated during the active phase and is usually indicated after 18 months from the onset of the disease, when the plaque has stabilized. The stabilization of the plaque is known as the quiescent phase. During the active phase, approximately 15-20% of patients can get spontaneous resolution of their disease. Therefore, injections initiated during the active phase are also discouraged by some because this may lead to further trauma as opposed to allowing for spontaneous resolution.

*Hypothesis:* BTX-A penile injections into Peyronie's plaques can significantly prevent scar formation and promote scar breakdown as evidenced by reduced penile curvature.

## **II. PURPOSE**

The purpose of this study is to establish the efficacy of botulinum toxin in treating Peyronie's disease.

## **III. DRUG INFORMATION**

BOTOX<sup>®</sup> is the brand name for Botulinum toxin type A. For this study's treatment injections, we will be using 100 units of BOTOX<sup>®</sup> in 10 cc of preservative free normal saline, or 10 cc of preservative free normal saline for placebo.

BOTOX<sup>®</sup> and Placebo will be provided by Allergan, Inc.

BOTOX<sup>®</sup> is a purified neurotoxin complex supplied as a sterile, vacuum dried purified botulinum toxin type A, produced from fermentation of Clostridium botulinum type A.

One unit of BOTOX<sup>®</sup> corresponds to the calculated median intraperitoneal lethal dose (LD 50) in mice. The specific activity of BOTOX<sup>®</sup> is approximately 20 units/nanogram of neurotoxin protein complex.

BOTOX<sup>®</sup> blocks neuromuscular transmission by binding to acceptor sites on motor or sympathetic nerve terminals, entering the nerve terminals, and inhibiting the release of acetylcholine. This inhibition occurs as the neurotoxin cleaves SNAP-25, a protein integral to the successful docking and release of acetylcholine from vesicles situated within nerve endings. When injected intramuscularly at therapeutic doses, BOTOX<sup>®</sup> produces partial chemical denervation of the muscle resulting in a localized reduction in muscle activity. In addition, the muscle may atrophy, axonal sprouting may occur, and extra-junctional acetylcholine receptors

may develop. There is evidence that reinnervation of the muscle may occur, thus slowly reversing muscle denervation produced by BOTOX<sup>®</sup>.

BOTOX<sup>®</sup> is not expected to be present in the peripheral blood at measurable levels following IM or intradermal injection at the recommended doses. The recommended doses of neurotoxin administered at each treatment session are not expected to result in systemic, overt distant clinical effects, i.e., muscle weakness, in patients without other neuromuscular dysfunction. However, some clinical systemic effects have been shown by a single fiber electromyography after IM doses of botulinum toxins appropriate to produce clinically observable local muscle weakness.

BOTOX<sup>®</sup> is contraindicated in the presence of infection at the proposed injection site(s), and in individuals with known hypersensitivity to any ingredient in the formulation.

BOTOX<sup>®</sup> is supplied in a single-use vial. Each vial contains 100 units of vacuum-dried Clostridium botulinum type A neurotoxin components.

Unopened vials of BOTOX<sup>®</sup> should be stored in a refrigerator (2° to 8° C) for up to 24 months (or the expiration date on the product label). Administer BOTOX<sup>®</sup> within four hours of reconstitution and within 30 minutes of drawing into syringe; during this period the reconstituted BOTOX<sup>®</sup> should be stored in a refrigerator (2° to 8° C).

Additional BOTOX<sup>®</sup> information is available in the BOTOX<sup>®</sup> Prescribing Information package insert.

#### **IV. ELIGIBILITY CRITERIA**

##### **A. Inclusion:**

1. Subjects with stable Peyronie's plaques.
2. Males at least 18 years of age
3. Prior history of failed penile injection therapies is allowed.
4. Must give informed consent.

##### **B. Exclusion:**

1. Subjects in the active phase of Peyronie's disease.
2. Subjects with less than 1 year history of Peyronie's disease.
3. Subjects taking oral medications for Peyronie's disease which include Trentol, Viagra, vitamin E, colchicines, L-arginine, and tamoxifen. There will be a 2 week wash-out period if patients are on these medications.
4. Subjects with more than 1 penile plaque will be excluded from the study.
5. Subjects with calcified plaques demonstrated by ultrasound will be excluded from the study.
6. Known allergy or sensitivity to any components of the study medication (botulinum toxin A), anesthetics, or any other product associated with the treatment and general study procedures.

7. Any medical condition or neuromuscular disorder that may put the patient at increased risk with exposure to botulinum toxin A (BTX-A), including myasthenia gravis, Eaton-Lambert syndrome, or amyotrophic lateral sclerosis.
8. Patient taking aminoglycosides or any drug known to interfere with neuromuscular transmission.
9. Patient has hemophilia or other clotting factor deficiencies or disorders that cause bleeding diathesis.
10. Patient must not be taking aspirin, non-steroidal anti-inflammatory drugs, or Coumadin for 7 or more days prior to Botox injection.
11. Episode of unstable angina pectoris, myocardial infarction, transient ischemic attack, or cerebrovascular accident within the past 6 months.

## V. DESIGN

This is a randomized, placebo-controlled, cross-over, single-center trial. Study drug is Botulinum toxin type A (BOTOX<sup>®</sup>). Subjects who meet the inclusion criteria for the study will be randomized to either the treatment or placebo arm.

**ARM 1 - Treatment:** Injection solution will consist of 100 units of BOTOX<sup>®</sup> in 10 cc of preservative free normal saline, or

**ARM 2 - Placebo:** Injection solution will consist of 10 cc preservative free normal saline.

The Week 16 Visit will be the end of the study participation for those subjects in Arm 1 and who did not develop ED (as defined as a drop in IIEF scores of more than 4 points from Baseline IIEF score). The Week 16 Visit will be the end of study participation for subjects in Arm 2 and who developed ED. For subjects in Arm 2, crossover to BOTOX treatment will begin after the Week 16 Visit by repeating the study schedule as for Week 0 to Week 16. Continuation visits at Months 6, 9, and 12 will occur for subjects in Arm 1 and who developed ED.

## VI. RANDOMIZATION PROCEDURES:

The subjects will be randomized to the arms as they are enrolled and meet eligibility criteria. The odd number (1, 3, 5...) of subjects will be in ARM 1 and even numbers (2, 4, 6...) of subjects will be in the ARM 2. The randomization scheme will not result in selection bias.

## VII. SCHEDULE OF EVENTS

PROCEDURE	Baseline (Pre-treatment)	Week 0 Clinic Visit	Week 2 Phone Visit	Week 4 Clinic Visit	Week 6 Phone Visit	Week 8 Clinic Visit	Week 10 Phone Visit	Week 12 Clinic Visit	Week 14 Phone Visit	<sup>1</sup> Week 16 Clinic Visit ( <sup>2</sup> End of Study) ( <sup>3</sup> Placebo Crossover)	<sup>4</sup> Month 6 Clinic Visit	<sup>4</sup> Month 9 Clinic Visit	<sup>4</sup> Month 12 Clinic Visit (End of Study)
Signed, written informed consent	X												
Medical history	X												
Physical examination	X									X	X	X	X
Blood pressure, pulse, O <sub>2</sub> saturation	X									X			
Penile injection: Caverject 20mcg/cc	X									X			
Penile curvature assessment & photos	X									X			
Penile ultrasound	X									X			
IIEF questionnaire	X									X			
Randomization	X												
Penile injection: BTX-A or <sup>3</sup> Placebo		X		X		X		X					
Collect AE information		X	X	X	X	X	X	X	X	X	X	X	X
Concomitant meds	X	X		X		X		X		X	X	X	X

<sup>1</sup>End of study for subjects receiving BOTOX and did not develop ED (as defined as a drop in IIEF scores of more than 4 points from Baseline IIEF score).

<sup>2</sup>End of study participation for subjects receiving placebo and develop ED.

<sup>3</sup>For subjects receiving placebo, crossover to BOTOX treatment will begin by repeating the study schedule as for Week 0 to Week 16.

<sup>4</sup>Continuation visits for subjects receiving BOTOX and developed ED.

## VIII. PROCEDURES

Subjects who meet the inclusion criteria for the study will be randomized to either the treatment or placebo arm. Prior to treatment, all subjects will have a penile injection with Caverject 20mcg/cc to induce a penile erection. During the erect state, penile curvature will be assessed, pictures will be taken for later measurement of penile curvature, and ultrasound will be used to assess penile blood flow and plaque size. A penile duplex with intercavernosal injections of a vasoactive substance is part of our standard care for Peyronies disease diagnosis. Subjects will also be asked to complete the International Index of Erectile Function (IIEF) questionnaire.

Injections will be performed using our standard protocol currently used for verapamil injections, but instead we will be using 100 units of BTX-A in 10cc of preservative free normal saline, or 10cc of preservative free normal saline for placebo and plaque breakdown injections. The standard injection procedure consists of the following:

1. Subjects will be explained the risks and benefits of the procedure and will give informed consent.
2. Blood pressure, pulse, and oxygen saturation will be monitored throughout the procedure.
3. A penile block with 10cc of lidocaine without epinephrine will be given, followed by an observation period of 10 minutes to assure no immediate adverse reaction to lidocaine.
4. Approximately 20 to 30 injections with a 20 gage needle will be given directly into the penile plaque. The skin will not be punctured with each injection, but the needle will move within the plaque. Injection solution will consist of 100 units of BTX-A in 10 cc of preservative free normal saline, or 10 cc of preservative free normal saline.
5. Subjects in the placebo arm will only receive 10 cc of preservative free normal saline.
6. Subjects will be monitored for 1 hour after the procedure to ensure that their vital signs are stable and that there are no signs of penile hematoma.
7. Safety will be assessed by following the subject closely for one hour after the procedure.
8. Subjects will be given strict instructions to call and return to the clinic or the ER for any adverse side effects.

Subjects randomized to ARM 1 will receive one injection of 10 cc preservative normal saline at study start (week 0), followed by 100 U Botox in 10cc saline at visit two (week 4), then saline injections at weeks 8 and 12, thus a total of 4 injections (1 saline, 1 Botox, 2 saline).

Subjects randomized to ARM 2 will receive one injection of 10cc preservative normal saline at Weeks 0, 4, 8 and 12.

All subjects will be telephoned two weeks after each injection to inquire on the occurrence of any adverse events. Subjects will be asked a general, non-direct question such as, "How have you been feeling since the last visit?" Direct questioning will then be done as appropriate.



At the completion of 16 weeks (4 weeks after last treatment), subjects will have a repeat penile injection of Caverject, penile pictures will be taken, and penile ultrasonography will be performed. Subjects will also be asked to complete the IIEF again.

The Week 16 Visit will be the end of the study participation for those subjects in Arm 1 and who did not develop ED (as defined as a drop in IIEF scores of more than 4 points from Baseline IIEF score). Subjects developing ED, will have continuation visits at Months 6, 9, and 12. At these visits, a complete physical will be done. Information about any adverse events and changes in concomitant medications will be collected. The subjects will complete the IIEF questionnaire.

If at the end of 16 weeks there is a significant improvement in the subjects treated with BTX-A as compared to the placebo arm, the men in the placebo arm will be given the option to cross over into the treatment arm and complete a 12 week course of BTX-A injections (1 saline injection, 1 Botox injection, 2 saline injections). For those in Arm 2 who develop ED, participation will end after the Week 16 visit.

## **IX. RISKS**

**BOTOX®:** It is expected that some participants may have some or all of the following side effects when given BOTOX®. Other side effects may occur which were not seen before. Side effects are usually temporary and manageable. However, it is possible they could cause serious disease or death. The study may include risks that are unknown at this time.

There have been rare reports of serious and/or immediate or even deadly abnormally sensitive reactions after treatment with BOTOX. These reactions include allergic reaction, skin rash, itching, swelling, and difficulty in breathing.

There have been rare reports of sudden death, sometimes associated with difficulty in swallowing or pneumonia. There have also been rare reports of heart problems (including irregular heart beats and heart attack, some resulting in death). Some of these patients were already at risk for heart disease. It is not known if BOTOX actually caused these problems.

It should not be used when infection is present at the injection site or in people known to be abnormally sensitive to BOTOX.

The following events have been observed since it has been marketed: skin rash, itching, and allergic reaction. In general, these side effects occur within the first week following injection and, while usually temporary, they may last several months. Pain, tenderness, or bruising around the injection site may also occur. Local weakness of the injected muscle(s) is expected. Weakness of nearby muscles may also occur due to spread of BOTOX.

BOTOX contains albumin, which comes from human blood. Although the blood is rigorously tested, there is an extremely remote risk for the transmission of viruses and similar infectious agents.

CAVERJECT®: Possible side effects of therapy with Caverject are penile pain after injection, usually mild to moderate in severity. A potentially serious reaction is priapism; therefore, patients should be instructed to seek medical attention if an erection last for more than 4 hours.

The injection can induce a small amount of bleeding at the site and a hematoma may form. There may be an occurrence of nodules or hard tissue in the penis, redness, and swelling.

Hypertension was reported in about 2% of patients. Headaches and dizziness were reported in 2% or less of patients. About 1% of the patients complained of backache. Upper respiratory infections were reported in 4% and flu-like symptoms in 2%. Sinusitis was reported in 2% and nasal congestion and coughs in 1%. Prostatic disorders were reported in 2%. Localized pain at injection site was reported in about 2% and trauma, such as, injuries, fractures, abrasions, lacerations, and dislocations were reported in 2%.

Less than 1% of patients in clinical studies reported the following events that were judged as possibly related to the use of Caverject: testicular pain and disorder, scrotal disorder, scrotal edema, hematuria, impaired urination, urinary frequency, urinary urgency, pelvic pain, hypotension, vasodilation, peripheral vascular disorder, supraventricular extrasystoles, vasovagal reaction, hypesthesia, non-generalized weakness, diaphoresis, rash, non-application site pruritus, skin neoplasm, nausea, dry mouth, increased serum creatinine, leg cramps, and mydriasis.

LIDOCAINE®: Adverse experiences with Lidocaine are, in general, dose-related and may result form high plasma levels caused by excessive dosage, rapid absorption or inadvertent intravascular injection, or may result from a hypersensitivity, idiosyncrasy or diminished tolerance on the part of the patient.

Central nervous system symptoms that may be experienced are lightheadedness, nervenousness, apprehension, euphoria, confusion, dizziness, drowsiness, tinnitus, blurred or double vision, vomiting, sensations of heat, cold or numbness, twitching, tremors, convulsions, unconsciousness, respiratory depression and arrest.

Cardiovascular manifestations are usually depressant and are characterized by bradycardia, hypotension, and cardiovascular collapse, which may lead to cardiac arrest.

Allergic reactions are characterized by cutaneous lesions, urticaria, edema, or anaphylactoid reactions. These reactions to Lidocaine are extremely rare.

The effect of the study treatments on the ability to have erections and to have intercourse is unknown. It is not known whether the treatments the subject receives in this study will worsen or will improve his ability to have intercourse

Additional risks that may be experience by subjects participating in this study are:

The risk of developing erectile dysfunction after these injections is unknown.

Inserting needles into the penis may be uncomfortable. Pain, tenderness, or bruising around the injection site may occur.

The ultrasound rarely results in physical discomfort but some anxiety before and during the procedure may be experienced.

Completing the questionnaire may cause some anxiety or embarrassment to the subject due to the personal nature of the questions.

The loss of confidentiality regarding research information is a possibility; although, the risk is very small.

## **X. CRITERIA FOR DISCONTINUING THE STUDY**

- A. Subjects unable to tolerate BTX-A due to side effects.
- B. Subjects can request removal from the study for any reason at any time.
- C. Subjects may be withdrawn at any time at the discretion of the investigator for safety, compliance, or other reasons.

A discontinuation occurs when an enrolled subject ceases participation in the study, regardless of the circumstances, prior to completing the protocol.

The reasons for a subject discontinuing from the study will be recorded in the Case Report Form.

## **XI. SAMPLE SIZE**

This will be a pilot study and therefore 10 subjects in each arm, for a total of 20 subjects, will allow us to determine if the therapy is effective. To allow for screen failures, 45 subjects are planned for screening.

## **XII. DATA ANALYSIS**

- A. The primary outcome measure will be:
  - 1. change in penile curvature, as measured by a protractor from pictures taken at baseline versus the end of treatment at 16 weeks
- B. Secondary outcomes will be measured objectively and subjectively.
- C. Objective measures will be:
  - 1. improvements in penile blood flow
  - 2. reduction in penile plaque size as seen on ultrasound
- D. Subjective measures will be:

1. changes in IIEF scores

As mentioned above, these objective and subjective measurements will be performed before and after the 16 week treatment.

Data will be analyzed using a t-test to compare differences between the two groups.

### **XIII. SAFETY MONITORING PLAN:**

This safety monitoring plan applies to the investigator-initiated clinical trials conducted at the Scott Department of Urology at Baylor College of Medicine. The safety monitoring plan sets forth mechanisms for reviewing and evaluating toxicity and any other study-relevant safety-related data for the investigator-initiated clinical trials. Such review and evaluation will ensure the safety of all study participants and the integrity of study data collected. The confidentiality of study data will be maintained at all times.

#### **A. Purpose:**

The Safety Monitoring Plan is meant to assure that this clinical investigation has a system for appropriate oversight and monitoring of the conduct of the clinical investigation. This oversight ensures the safety of the study subjects and the validity and integrity of the data.

#### **B. Protocol Monitoring:**

The PI will be responsible of monitoring the safety and efficacy of the trial, executing the Safety Monitoring Plan, and complying with the reporting requirements. Monitoring will be performed on a regular basis. All clinical and safety data including AE's, toxicities, and responses will be reviewed by the PI, investigators and research staff at regularly scheduled research meetings. The PI will provide a summary of the Safety Monitoring Plan findings to the appropriate regulatory authorities on an annual basis as part of the progress report. The progress report will include participant demographics, expected versus actual recruitment rates, summary of AEs and SAEs, any QA or regulatory issues that occurred during the past year, and any actions or changes with respect to the protocol.

#### **C. Data Collection:**

Data will be collected using the protocol's case report forms. Participants will be identified on the forms by their study ID number. The clinical study coordinator of the trial will maintain the codes that link the name of the participant to their study ID number. The study coordinator will maintain the code in a secured cabinet and the code will be kept confidential. Only the clinical study coordinator and PI can access and view the codes. Data quality will be monitored by random inspection of the completed forms by a member of the Scott Department of Urology's Research

Administration QA unit. Any problems detected by QA personnel will be discussed with the PI.

**D. Safety Monitoring:**

During the treatment phase of the study, participants will be asked about AEs at each visit. The investigators and/or the study coordinator will document all AEs. All AEs occurring during the course of the study will be collected, documented, and reported to the PI. AEs will be followed to the point of a satisfactory resolution. Study participants may have their study drug discontinued or they may be withdrawn from the study if the PI determines it is the best decision in order to protect the safety of the participant. Additional AE information is contained in Appendix II - Adverse Event Reporting.

**XIV. ADVERSE EVENT REPORTING**

Adverse Events will be reported in accordance to all applicable FDA, ICH, and IRB rules, regulations, and guidelines.

**XV. Data Handling and Record Keeping**

**A. Case Report Forms**

Protocol-specific data will be collected on Case Report Forms (CRFs). The completed dataset should not be made available in any form to third parties, except for authorized representatives of appropriate Health/Regulatory Authorities, without written permission from BCM.

**B. Record Retention**

To enable evaluations and/or audits from Health Authorities/BCM, the investigator agrees to keep records, including the identity of all participating patients (sufficient information to link records; e.g., hospital records), all original signed informed consent forms, copies of all CRF's, and detailed records of drug disposition. To comply with international regulations, the records should be retained by the investigator in compliance with regulations.

**XVI. Protocol Changes**

If it is necessary for the study protocol to be amended, the amendment will be submitted to the BCM IRB for approval. Amended procedures will not be in effect until after IRB approval has been given. The principal investigator is responsible for the distribution of

the approved documents to the staff. The FDA guidelines for submission of an amended protocol will be used for notification purposes.

Revisions to questionnaires or CRFs will not require IRB or FDA approval; therefore, these revisions will not be reported.

## **XVII. Ethics and Good Clinical Practice**

This study must be carried out in compliance with the protocol and the principles of Good Clinical Practice, as described in Novartis standard operating procedures and:

- ICH Harmonized Tripartite Guidelines for Good Clinical Practice 1996. Directive 91/507/EEC, The Rules Governing Medicinal Products in the European Community.
- US 21 Code of Federal Regulations dealing with clinical studies (including parts 50 and 56 concerning informed consent and IRB regulations).
- Declaration of Helsinki and amendments, concerning medical research in humans (Recommendations Guiding Physicians in Biomedical Research Involving Human Subjects).

The investigator agrees to adhere to the instructions and procedures described in it and thereby to adhere to the principles of Good Clinical Practice that it conforms to.

### **A. Institutional Review Board (IRB) and Other Institutional Review Committees**

Before implementing this study, the protocol, the proposed informed consent form and other information to subjects, must be reviewed by a properly constituted and other institutional review committees, as required. A signed and dated statement that the protocol and informed consent document(s) have been approved by the IRB and committees will be provided to the FDA in a general correspondence submission.

### **B. Informed Consent Process**

The investigator or his designated personnel must explain to each subject (or legally authorized representative) the nature of the study, its purpose, the procedures involved, the expected duration, the potential risks and benefits involved and any discomfort it may entail. Each subject must be informed that participation in the study is voluntary and that he/she may withdraw from the study at any time and that withdrawal of consent will not affect his/her subsequent medical treatment or relationship with the treating physician. Informed consent will be obtained in every patient prior to performing a biopsy or any protocol-related procedures or tests.

This informed consent should be given by means of a standard written statement, written in non-technical language. The subject should read and consider the statement before signing and dating it, and should be given a copy of the signed document. If the subject cannot read or sign the documents, oral presentation may be made or

signature given by the subject's legally appointed representative, if witnessed by a person not involved in the study, mentioning that the patient could not read or sign the documents. No patient can enter the study before his informed consent has been obtained. The original signed informed consent form will be kept with the research study documents, a copy will be given to the subject, and a copy will be placed in the subject's medical chart.

### **C. Declaration of Helsinki**

The investigator must conduct the trial in accordance with the principles of the Declaration of Helsinki. Copies of the Declaration of Helsinki and amendments will be provided upon request or can be accessed via the website of the World Medical Association at [http://www.wma.net/e/policy/17-c\\_e.html](http://www.wma.net/e/policy/17-c_e.html).

## **XVIII. CONFIDENTIALITY**

Each subject will be assigned a unique, consecutive three-digit identification number (i.e., 001, 002, ...). The study number will be utilized for identification of the subject throughout the study. The clinical study coordinator of the trial will maintain the code that links the name of the participant to their study ID number. The study coordinator will maintain the code in a secured cabinet and the code will be kept confidential. Only the clinical study coordinator and PI can access and view the codes.

The research records will be maintained in the Scott Department of Urology. The computers used for this study are password protected. The data will be kept by the clinical coordinator in a secure locked area. Areas are protected after hours by an electronic door locking systems. The Scott Department of Urology adheres to the HIPAA guidelines.

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# APPENDICES

# **APPENDIX I**

## **IEF QUESTIONNAIRE**

## International Index of Erectile Function (IIEF) Questionnaire\*

Study ID: H-22411: BOTOX in Peyronie's Disease Date: \_\_\_\_\_ Visit #: \_\_\_\_\_

**Please circle your answer**

1. Over the past 4 weeks, how often were you able to get an erection during sexual activity?

No sexual activity .....	0
Almost never/never .....	1
A few times (much less than half of the time).....	2
Sometimes (about half of the time) .....	3
Most times (much more than half of the time).....	4
Almost always/always .....	5
  
2. Over the past 4 weeks when you had erections with sexual stimulation, how often were your erections hard enough for penetration?

No sexual activity .....	0
Almost never/never .....	1
A few times (much less than half of the time).....	2
Sometimes (about half of the time) .....	3
Most times (much more than half of the time).....	4
Almost always/always .....	5
  
3. Over the past 4 weeks when you attempted sexual intercourse, how often were you able to penetrate (enter) your partner?

Did not attempt intercourse .....	0
Almost never/never .....	1
A few times (much less than half of the time).....	2
Sometimes (about half of the time) .....	3
Most times (much more than half of the time).....	4
Almost always/always .....	5
  
4. Over the past 4 weeks during intercourse, how often were you able to maintain your erection after you had penetrated (entered) your partner?

Did not attempt intercourse .....	0
Almost never/never .....	1
A few times (much less than half of the time).....	2
Sometimes (about half of the time) .....	3
Most times (much more than half of the time).....	4
Almost always/always .....	5
  
5. Over the past four weeks, during sexual intercourse, how difficult was it to maintain your erection to completion of intercourse?

Did not attempt intercourse .....	0
Extremely difficult .....	1
Very difficult .....	2
Difficult .....	3
Slightly difficult .....	4
Not difficult .....	5
  
6. Over the past four weeks, how many times have you attempted sexual intercourse?

No attempts.....	0
One to two attempts .....	1
Three to four attempts.....	2
Five to six attempts .....	3
Seven to ten attempts .....	4
Eleven or more attempts .....	5
  
7. Over the past four weeks when you attempted sexual intercourse, how often was it satisfactory for you?

Did not attempt intercourse .....	0
Almost never/never .....	1
A few times (much less than half of the time).....	2
Sometimes (about half of the time) .....	3
Most times (much more than half of the time).....	4
Almost always/always .....	5

## International Index of Erectile Function (IIEF) Questionnaire\*

8. Over the past four weeks, how much have you enjoyed sexual intercourse?

- No intercourse..... 0
- No enjoyment..... 1
- Not very enjoyable ..... 2
- Fairly enjoyable..... 3
- Highly enjoyable..... 4
- Very highly enjoyable ..... 5

9. Over the past four weeks, when you had sexual stimulation or intercourse, how often did you ejaculate?

- No sexual stimulation/intercourse ..... 0
- Almost never/never ..... 1
- A few times (much less than half of the time)..... 2
- Sometimes (about half of the time) ..... 3
- Most times (much more than half of the time) ..... 4
- Almost always/always ..... 5

10. Over the past four weeks when you had sexual stimulation or intercourse, how often did you have the feeling of orgasm or climax?

- No sexual stimulation/intercourse ..... 0
- Almost never/never ..... 1
- A few times (much less than half of the time)..... 2
- Sometimes (about half of the time) ..... 3
- Most times (much more than half of the time) ..... 4
- Almost always/always ..... 5

11. Over the past four weeks, how often have you felt sexual desire?

- Almost never/never ..... 1
- A few times (much less than half of the time)..... 2
- Sometimes (about half of the time) ..... 3
- Most times (much more than half of the time) ..... 4
- Almost always/always ..... 5

12. Over the past four weeks, how would you rate your level of sexual desire?

- Very low/none at all..... 1
- Low ..... 2
- Moderate ..... 3
- High..... 4
- Very high..... 5

13. Over the past four weeks, how satisfied have you been with your overall sex life?

- Very dissatisfied..... 1
- Moderately dissatisfied..... 2
- About equally satisfied and dissatisfied..... 3
- Moderately satisfied ..... 4
- Very satisfied ..... 5

14. Over the past four weeks, how satisfied have you been with your sexual relationship with your partner?

- Very dissatisfied..... 1
- Moderately dissatisfied..... 2
- About equally satisfied and dissatisfied..... 3
- Moderately satisfied ..... 4
- Very satisfied ..... 5

15. Over the past four weeks, how do you rate your confidence that you could get and keep an erection?

- Very low ..... 1
- Low ..... 2
- Moderate ..... 3
- High..... 4
- Very high..... 5

\*RC Rosen, A Riley, G Wagner et al. The international index of erectile dysfunction (IIEF): a multidimensional scale for assessment of erectile dysfunction. Urology 1997 49: 822-30.

## International Index of Erectile Function (IIEF) Questionnaire\*

Study ID: \_\_\_\_\_ Date: \_\_\_\_\_ Visit #: \_\_\_\_\_

### **Please circle your answer**

1. Over the past 4 weeks, how often were you able to get an erection during sexual activity?

- No sexual activity ..... 0
- Almost never/never ..... 1
- A few times (much less than half of the time)..... 2
- Sometimes (about half of the time)..... 3
- Most times (much more than half of the time) ..... 4
- Almost always/always ..... 5

2. Over the past 4 weeks when you had erections with sexual stimulation, how often were your erections hard enough for penetration?

- No sexual activity ..... 0
- Almost never/never ..... 1
- A few times (much less than half of the time)..... 2
- Sometimes (about half of the time)..... 3
- Most times (much more than half of the time) ..... 4
- Almost always/always ..... 5

3. Over the past 4 weeks when you attempted sexual intercourse, how often were you able to penetrate (enter) your partner?

- Did not attempt intercourse ..... 0
- Almost never/never ..... 1
- A few times (much less than half of the time)..... 2
- Sometimes (about half of the time)..... 3
- Most times (much more than half of the time) ..... 4
- Almost always/always ..... 5

4. Over the past 4 weeks during intercourse, how often were you able to maintain your erection after you had penetrated (entered) your partner?

- Did not attempt intercourse ..... 0
- Almost never/never ..... 1
- A few times (much less than half of the time)..... 2
- Sometimes (about half of the time)..... 3
- Most times (much more than half of the time) ..... 4
- Almost always/always ..... 5

5. Over the past four weeks, during sexual intercourse, how difficult was it to maintain your erection to completion of intercourse?

- Did not attempt intercourse ..... 0
- Extremely difficult ..... 1
- Very difficult..... 2
- Difficult ..... 3
- Slightly difficult..... 4
- Not difficult ..... 5

6. Over the past four weeks, how many times have you attempted sexual intercourse?

- No attempts ..... 0
- One to two attempts ..... 1
- Three to four attempts ..... 2
- Five to six attempts ..... 3
- Seven to ten attempts ..... 4
- Eleven or more attempts ..... 5

7. Over the past four weeks when you attempted sexual intercourse, how often was it satisfactory for you?
- Did not attempt intercourse ..... 0
  - Almost never/never ..... 1
  - A few times (much less than half of the time)..... 2
  - Sometimes (about half of the time)..... 3
  - Most times (much more than half of the time) ..... 4
  - Almost always/always ..... 5
8. Over the past four weeks, how much have you enjoyed sexual intercourse?
- No intercourse..... 0
  - No enjoyment ..... 1
  - Not very enjoyable..... 2
  - Fairly enjoyable ..... 3
  - Highly enjoyable ..... 4
  - Very highly enjoyable ..... 5
9. Over the past four weeks, when you had sexual stimulation or intercourse, how often did you ejaculate?
- No sexual stimulation/intercourse..... 0
  - Almost never/never ..... 1
  - A few times (much less than half of the time)..... 2
  - Sometimes (about half of the time)..... 3
  - Most times (much more than half of the time) ..... 4
  - Almost always/always ..... 5
10. Over the past four weeks when you had sexual stimulation or intercourse, how often did you have the feeling of orgasm or climax?
- No sexual stimulation/intercourse..... 0
  - Almost never/never ..... 1
  - A few times (much less than half of the time)..... 2
  - Sometimes (about half of the time)..... 3
  - Most times (much more than half of the time) ..... 4
  - Almost always/always ..... 5
11. Over the past four weeks, how often have you felt sexual desire?
- Almost never/never ..... 1
  - A few times (much less than half of the time)..... 2
  - Sometimes (about half of the time)..... 3
  - Most times (much more than half of the time) ..... 4
  - Almost always/always ..... 5
12. Over the past four weeks, how would you rate your level of sexual desire?
- Very low/none at all ..... 1
  - Low..... 2
  - Moderate ..... 3
  - High..... 4
  - Very high ..... 5
13. Over the past four weeks, how satisfied have you been with your overall sex life?
- Very dissatisfied ..... 1
  - Moderately dissatisfied..... 2
  - About equally satisfied and dissatisfied..... 3
  - Moderately satisfied ..... 4
  - Very satisfied..... 5
14. Over the past four weeks, how satisfied have you been with your sexual relationship with your partner?
- Very dissatisfied ..... 1
  - Moderately dissatisfied..... 2
  - About equally satisfied and dissatisfied..... 3
  - Moderately satisfied ..... 4
  - Very satisfied..... 5

15. Over the past four weeks, how do you rate your confidence that you could get and keep an erection?

- Very low ..... 1
- Low..... 2
- Moderate ..... 3
- High..... 4
- Very high ..... 5

\*RC Rosen, A Riley, G Wagner et al. The international index of erectile dysfunction (IIEF): a multidimensional scale for assessment of erectile dysfunction. Urology 1997 49: 822-30.

# **APPENDIX II**

**SCOTT DEPARTMENT OF UROLOGY  
BAYLOR COLLEGE OF MEDICINE**

**QUALITY ASSURANCE PROGRAM GUIDELINES**



**SCOTT DEPARTMENT OF UROLOGY**  
**BAYLOR COLLEGE OF MEDICINE**  
**QUALITY ASSURANCE PROGRAM GUIDELINES**

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Research Administrator

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Manager, Regulatory Affairs

Research Administration  
713-798-9199

March 24, 2004

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**SCOTT DEPARTMENT OF UROLOGY**  
**BAYLOR COLLEGE OF MEDICINE**  
**QUALITY ASSURANCE PROGRAM GUIDELINES**

**Quality Assurance:** All actions taken to ensure that standards and procedures are adhered to and that services meet performance requirements. The planned systematic activities necessary to ensure that a system conforms to established requirements. The policy, procedures and systematic actions established in an enterprise for the purpose of providing and maintaining a specified degree of confidence in data integrity and accuracy throughout the lifecycle of the data which includes input, update, manipulation, and output.

**1.0 PURPOSE**

The purpose of the quality assurance/audit program is to: 1.) Enhance the delivery of accurate and reliable clinical trials data and results; 2.) Verify the accuracy of data; 3.) Verify that the 'in house clinical trials' program of the Scott Department of Urology is in compliance with protocol and regulatory requirements; and 4.) Provide educational support to the clinical research staff regarding issues related to data quality, data management and other aspects of quality assurance.

**2.0 QUALITY ASSURANCE AUDITS**

**2.1 Yearly Audit**

Each "in house clinical trial" will be audited yearly. Each clinical trial will remain at risk for random audit. The yearly audit will consist of:

**2.1.1** Sponsor/Monitor Audit

**2.1.2** Investigator File Audit

**2.1.3** Informed Consent Audit

**2.1.4** Data Collection

The research coordinator is required to produce the following data relevant to each patient's research binder:

2.1.4.1 Clinical trial-specific case report forms

2.1.4.2 Hospital charts, or legible copies.

2.1.4.3 Clinic (outpatient) charts.

2.1.4.4 Operative, pathology and radiotherapy reports.

2.1.4.5 Documentation that the Institutional Review Board (IRB) has initially and annually reviewed and approved each protocol on the list including any protocol modifications.

- 2.1.4.6 Source documents for all data entered on the case report forms.
- 2.1.4.7 Copies of the signed and dated consent forms for each patient.
- 2.1.4.8 Physicians order for vector administration or drug administration as applicable.
- 2.1.4.9 Copies of the protocols including model consent forms.
- 2.1.4.10 Copies of all adverse events submitted to the IRB
- 2.1.4.11 Copies of all amendments to the original protocol

## **2.2 Quality Assurance Audit Checklist**

A Quality Assurance Audit Checklist has been developed to assist research coordinators to maintain accurate research binders.

## **2.3. Quality Assurance Review Form**

A Quality Assurance Review Form has been developed for use when auditing a research binder. It is used as an all-inclusive review of each research binder.

## **3.0 CONDUCT OF A QUALITY ASSURANCE AUDIT**

The purpose of the audit is to assure the accuracy of the data and to verify compliance with protocol and regulatory requirements. The audit is conducted in three parts:

### **3.1 Patient Case Review**

The major objective of the audit program is to verify study data that could affect the interpretation of primary study endpoints. This is done by comparing the data records with the patient's primary record to evaluate compliance to protocol requirements and accuracy in data reporting. This review will entail examination of the following criteria for each participant:

#### **3.1.1 Eligibility**

Verify all eligibility criteria, stratification factors and required prestudy parameters to confirm patient met all eligibility criteria as specified by the protocol.

#### **3.1.2. Treatment Compliance with Protocol**

Establish in the primary record the patient's actual height and weight and body surface area. Verify doses, dates of treatment, and administration were according to protocol specifications.

#### **3.1.3 Disease Outcome/Response Determination**

Verify that disease outcome was evaluated according to protocol. Responses (PR, CR) should be verified through review of x-rays, scans, pathology reports, and records of physical examinations.

#### **3.1.4 Toxicity Assessment**

Verify that toxicities were assessed according to protocol by use of required baseline and follow-up studies. Verify that toxicities were properly graded and accurately reported and any Adverse Events

were filed. All drug-related toxicities must be coded and recorded according to the Group's toxicity criteria.

### **3.1.5 Data Quality**

The primary record will be compared to the flow sheets to determine accuracy in the reporting of eligibility, treatment administration, reporting and coding of toxicities, and response assessment. All laboratory results required by protocol must be reported on the flow sheets, or reported as not having been done. Initial form sets, pathology material, flowsheets, etc. must be included in the research binder.

## **3.2 Regulatory Requirements**

### **3.2.1 Consent Form**

Consent forms must be the protocol specific consent form approved by the Institutional Review Board (IRB), be dated and signed prior to registration, and contain applicable elements outlines in Title 45, Code of Federal Regulations, Part 46, Protection of Human Subjects. Any significant new findings that may relate to the subject's willingness to continue participation should be provided to the subject in accordance with Section 46.116(b)(5).

### **3.2.2 IRB Approvals**

Minutes of the IRB meetings or detailed letters from the IRB will be accepted as documentation of IRB review. Documentation will be reviewed to ensure full initial IRB approval of the protocol prior to patient registration, annual re-approval of the protocol, and full board IRB approval of designated protocol modifications. There must not be more than 365 days between annual approvals and protocols must receive annual approval as long as data is being gathered on patients.

## **3.3 Investigational Drug Accountability**

### **Drug Accountability Record Maintenance**

As of February 15, 1983, the NCI has required that drug accountability record forms be maintained by all institutions conducting clinical trials with NCI supplied investigational drugs. Institutions must use NCI forms to account for all drugs that are supplied by the NCI (including commercial drugs). Auditors are required to inspect the drug logs and tour the area where the investigational drugs are stored.

### **3.3.1 Drug Logs**

This review verifies that the drug logs are maintained according to the NCI instructions. The shipping receipts indicating the protocol numbers, the quantity of drug shipped and the drug lot numbers are compared to the drug log for accuracy. Drug handling procedures are reviewed to assure the return of expired drugs to the NCI drug repository with the appropriately completed form, disposal of any unused portions of drugs, and transfer or return of drugs from closed protocols. If any drugs have been dispensed to a satellite, these records will also be audited. The dates and dosages recorded on the flowsheets will then be compared to the drug logs for the patients selected for the drug audit.

### **3.3.2 On-Site Audit**

During the on-site audit, a tour of the storage facilities will be conducted. The area in which the drugs are stored should be a separate, secure, limited-access area; and the drugs must be stored at the correct temperature and must be identified by protocol number. A physical inventory will be done to verify the quantity, and lot numbers will be compared with the drug logs for accuracy.

## **4.0 DEFINITIONS AND EXAMPLES OF DEVIATIONS FOR PATIENT CASE REVIEW**

### **4.1 Major Deviation**

Variance from protocol-specified procedures that makes the resulting data questionable.

#### **4.1.1 Eligibility**

**4.1.1.1** Patient did not meet eligibility criteria as specified by protocol.

**4.1.1.2** Unable to confirm eligibility due to missing documentation.

#### **4.1.2 Treatment**

**4.1.2.1** Incorrect agent/treatment used.

**4.1.2.2** Additional agent/treatment used which is not permitted by protocol.

**4.1.2.3** Incorrect dose deviations (greater than +/- 10%).

**4.1.2.4** Unjustified dose modifications or failure to modify doses according to protocol.

**4.1.2.5** Treatment doses incorrectly administered, calculated, or documented.

**4.1.2.6** Unjustified delays in treatment.

#### **4.1.3 Disease Outcome/Response Assessment**

**4.1.3.1** Failure to assess disease status according to the required protocol guidelines.

**4.1.3.2** Repetitive or substantial inaccuracy in the assessment of tumor response.

**4.1.3.3** Substantial inaccuracy in the detection of cancer (as in prevention study) or determination of cancer progression.

**4.1.3.4** Response (PR, CR) cannot be verified.

**4.1.3.5** Failure to detect cancer (as in a prevention study) or failure to identify cancer progression

#### **4.1.4 Toxicity**

**4.1.4.1** Failure to obtain the required protocol baseline and follow-up studies required to effectively assess toxicity.

**4.1.4.2** Unreported major toxicity (Grade 4 or 5).

**4.1.4.3** Repetitive failure to report Grade 2 - 3 toxicities.

**4.1.4.4** Serious or repetitive failure to properly characterize toxicity or grade.

**4.1.4.5** Failure to file required NCI Adverse Event Reports according to the protocol and NCI Guidelines if applicable.

#### 4.1.5 General Data Quality

- 4.1.5.1 Unacceptable level of missing documentation (for example, missing charts, repetitive failure to obtain protocol specified laboratory tests or diagnostic studies).
- 4.1.5.2 Frequent inaccuracies or errors in submitted data.
- 4.1.5.3 Use of white out in the primary record.
- 4.1.5.4 Delinquent data
  - 4.1.5.4.1 greater than 3 months for initial form sets and pathology materials
  - 4.1.5.4.2 greater than 6 months for follow-up data while patient on treatment
  - 4.1.5.4.3 greater than one year for follow-up data for first two years patient is off treatment.

#### 4.1.6 Informed Consent

- 4.1.6.1 Consent form missing.
- 4.1.6.2 Consent form not signed and dated by patient.
- 4.1.6.3 Consent form signed after patient started treatment.
- 4.1.6.4 Consent form not the current IRB-approved version at the time of registration.
- 4.1.6.5 Consent form does not include updates or information distributed as an amendment to the protocol.
- 4.1.6.6 Consent form does not include required elements.

#### 4.2 Minor Deviations

Deviations that do not affect the outcome or interpretation of the study and are not described above as major deviations. An unacceptable frequency of minor deviations will be treated as a major deviation.

#### 5.0 QUALITY ASSURANCE CASE REVIEW FORM

**SCOTT DEPARTMENT OF UROLOGY**

**QUALITY ASSURANCE CASE REVIEW FORM**

Patient # \_\_\_\_\_ Protocol # \_\_\_\_\_ Disease \_\_\_\_\_

Investigator \_\_\_\_\_

**ELIGIBILITY**

No	Major	Minor	NA
----	-------	-------	----

Patient did not meet all eligibility criteria as specified by protocol.				
Documentation missing; unable to confirm eligibility.				
Other				

**TREATMENT**

Incorrect agent/treatment used.				
Additional agent/treatment used which is not permitted by protocol.				
Incorrect dose deviations (greater than +/- 10%).				
Unjustified dose modifications.				
Treatment doses incorrectly administered, calculated, or documented.				
Unjustified delays in treatment.				
Other				

**DISEASE OUTCOME/RESPONSE DETERMINATION**

Inaccurate documentation of initial sites of involvement.				
Tumor measurements/eval of status of disease not performed according to protocol.				
Protocol-directed response criteria not followed.				
Claimed response (CR, PR) cannot be verified.				
Failure to detect cancer (prevention study) or failure to identify cancer progression.				
Other				

**TOXICITY**

Grades/types or dates/duration of serious toxicities inaccurately recorded.				
Toxicities cannot be substantiated.				
Follow-up studies necessary to assess toxicities not performed.				
Failure to report an Adverse Event.				
Recurrent under or over-reporting of toxicities.				
Other				

**DATA QUALITY**

**Date of Last Contact:**

Recurrent missing documentation.				
Protocol-specified laboratory tests not documented.				
Protocol-specified diagnostic studies not documented.				
Frequent data inaccuracies.				
Delinquent data submission.				



CONSENT FORM

Date Signed: \_\_\_\_\_

Consent form missing.				
Consent form not signed and dated by patient.				
Consent form signed after patient started on treatment.				
Consent form does not contain all required signatures.				
Consent form used was not current IRB-approved version at the time of patient registration.				
Consent form not protocol specific.				
Consent form does not include updates or information required by IRB				
Other (specify)				

**NOTE: "No" = OK. "Yes" = Major or Minor. All responses checked other than "No" must be explained.**

\_\_\_\_\_  
Auditor's Printed Name

\_\_\_\_\_  
Auditor's Signature

\_\_\_\_\_  
Date

\_\_\_\_\_  
Principal Investigator's Printed Name

\_\_\_\_\_  
Principal Investigator's Signature

\_\_\_\_\_  
Date

**6.0 IRB REVIEW FORM**

**Protocol #** \_\_\_\_\_

**No. of Patients** \_\_\_\_\_

**Initial IRB Approval** **Date:** \_\_\_\_\_

**Continuing review** **Date:** \_\_\_\_\_

<b><u>Amendment approvals</u></b>	<b><u>Amendment Version</u></b>	<b><u>Date of Approval</u></b>
_____	_____	_____
_____	_____	_____
_____	_____	_____

**MAJOR IRB Deficiency**

Protocol never approved by IRB	
Initial IRB approval documentation missing	
Initial IRB approval by expedited review	
Expedited approval for other than approved exceptions	
Registration and/or treatment prior to IRB approval	
Re-approval delayed > 30 days but < 1 year	
Registration of pt during a period of delayed re-approval	
Missing re-approval	
Expired re-approval	
Reportable adverse events not reported to IRB	
Lack of full board IRB approval of designated protocol modifications within 4 months	

**LESSER IRB Deficiency**

Re-approval delayed < 30 days	
Delayed re-approvals for closed protocols with all patients on follow-up	

**This list does not represent an all inclusive list of major and lesser deficiencies.**

**Comments:** \_\_\_\_\_

**IRB Assessment:** \_\_\_\_\_

\_\_\_\_\_  
Principal Investigator's Signature

\_\_\_\_\_  
Date

**7.0 INVESTIGATIONAL DRUG ACCOUNTABILITY FORM**

1 = Yes      2 = No      3 = Not Applicable

Case# \_\_\_\_\_

Protocol # \_\_\_\_\_

- 1. NCI Drug Accountability Record Form (DARF) in use? \_\_\_\_\_
  - A. Completely and correctly filled out? \_\_\_\_\_
  - B. Protocol and drug specific? \_\_\_\_\_
  - C. Satellite records accounted for? \_\_\_\_\_
  - D. NCI logs kept as primary transaction record? \_\_\_\_\_
  - E. Physician order for gene vector \_\_\_\_\_
  - F. Release of GMP vector \_\_\_\_\_
  - G. Balance on log matches physical inventory? \_\_\_\_\_
  - H. Random patients cross-checked with log? \_\_\_\_\_
- 2. Storage
  - A. Identified by protocol number? \_\_\_\_\_
  - B. Stored in limited-access, secured area? \_\_\_\_\_
- 3. Drug order receipts kept? \_\_\_\_\_
- 4. Drugs returned to the NCI and/or other transferred correctly? \_\_\_\_\_

Comments: \_\_\_\_\_

\_\_\_\_\_

\_\_\_\_\_  
Principal Investigator's Signature

\_\_\_\_\_  
Date

**8.0 QUALITY ASSURANCE AUDIT CHECKLIST**

**PATIENT'S NAME** \_\_\_\_\_ **PATIENT'S #** \_\_\_\_\_

**PROTOCOL #** \_\_\_\_\_

**INSTITUTIONAL REVIEW BOARD (IRB) APPROVAL:**

- \_\_\_\_\_ Documentation of IRB approval prior to the registration and treatment of the patient.
- \_\_\_\_\_ Annual IRB approvals.
- \_\_\_\_\_ Protocol modification approvals.

**CONSENT FORM:** A copy of the consent dated and signed by the patient.

**PRIMARY SOURCE DOCUMENTATION:**

The primary record must verify the data reported regarding study parameters.

- |  |                             |
|--|-----------------------------|
| _____ Hospital chart, or legible copies. | _____ Operative reports     |
| _____ Clinic chart, or legible copies.   | _____ Pathology reports.    |
| _____ X-rays, scans and reports.         | _____ Radiotherapy records. |
| _____ Other special studies.             | _____ Chemotherapy records. |

**RESEARCH RECORDS:**

- |  |   |
|--|---|
| _____ Eligibility checklist (If applicable). | _____ Special Forms.                                |
| _____ Prestudy form.                         | _____ Off-study form.                               |
| _____ Study specific flow sheets.            | _____ Copy of the protocol including model consent. |

**INVESTIGATIONAL DRUG ACCOUNTABILITY RECORD FORMS:**

- |                                   |                                   |
|-----------------------------------|-----------------------------------|
| _____ Control and Satellite DARFs | _____ Copies of Return form       |
| _____ Copies of Transfer forms    | _____ Copies of Shipping receipts |

\_\_\_\_\_  
Principal Investigator Signature \_\_\_\_\_  
Date

## 9.0 PREPARING FOR A QUALITY ASSURANCE AUDIT

The best time to begin preparing for an audit is just prior to registering a patient to a study.

### 9.1 IRB Approval

Confirming that the **IRB** has approved the protocol prior to registration.

### 9.2 Consent Form

Confirming that the patient has signed the most current IRB approved **consent form**. Keep a copy of the signed and dated consent form in the research record.

### 9.3 Eligibility Criteria

Verifying in the medical record all the prestudy **required data** as specified by the eligibility criteria and the study calendar.

## 10. HELPFUL HINTS

- 10.1 Copy the source documentation for the data reported as you abstract the data from the patient's primary record. This could possibly prevent a discrepancy for not being able to document the data reported when reviewed by auditors.
- 10.2 Approximately four weeks prior to the audit, you will receive the list of cases to be audited.
- 10.3 Thoroughly review the protocol for the eligibility criteria, study parameters, treatment requirements and response definitions.
- 10.4 For investigational drug accountability audit, notify the pharmacist, or the person responsible for the drug logs. Be sure the shipping receipts, return forms, transfer forms and drug logs will be available for the audit. Prepare for a tour of the area where the drugs are stored.
- 10.5 Notify the IRB Chairperson that you need documentation of initial and annual approval along with protocol modification approvals for each protocol on the list of cases. This documentation may be in the form of IRB letters of approval from the IRB Chairperson and/or minutes of the IRB meetings.
- 10.6 Once the source documentation is available, compare the data sheets with the medical records for accuracy, paying close attention to dates.
- 10.7 Clearly identify the data in the medical records to facilitate quick retrieval during the audit. It is suggested using colored tabs indicating treatment cycles, dates or week numbers. Be creative - the important point is for you to quickly find the documentation as requested by the auditors.
- 10.8 Be available all day to assist the auditors.
- 10.9 If the original medical records are not available, legible copies may be used.