Effects of Botox in Obstructed Defecation Syndrome

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Effects of Type A botulinum toxin in obstructed defecation syndrome: a Phase II randomized, parallel group, triple-blind, placebo- controlled trial

I. BACKGROUND AND SIGNIFICANCE

a. Historical background

Constipation represents one of the five most common physician diagnoses for gastrointestinal disorders[1]. Obstructed defecation syndrome (ODS) accounts for 30%-50% of all patients with constipation and its prevalence, health care costs and impact on the quality of life can be assessed indirectly from data available on constipation[2].

A 2011 review and meta-analysis of chronic idiopathic constipation worldwide identified a pooled global prevalence of 14%[2]. Another recent review on the epidemiology of chronic constipation identified a median prevalence of 16% (ranging from 0.7%-79%) in adults overall and 33.5% in adults aged 60 to 101 years[3]. In North America, over 63 million people met the Rome II criteria for constipation[8] .

Although only a minority of patients suffering from constipation seeks medical advice[4], constipation consumes significant health care resources because its prevalence is high[10]. The most recent data from the National Ambulatory Medical Care Survey and the National Hospital Ambulatory Medical Care Survey show that the number of ambulatory visits for constipation has doubled over a ten-year period[5]. From 1997 to 2006, a total of 52.7 million patient visits in the U.S. were related to constipation. The annual direct medical costs for constipation were estimated to exceed $230 million[6-7]. Recent studies suggest that among patients with constipation in the community, quality of life scores were comparable to those suffering from depression, hypertension and diabetes[9] .

Symptoms of constipation can be secondary to mechanical obstructions of the colon, drug side effects, and neurologic or metabolic disturbances[16]. Most frequently, however, constipation is caused by disordered function of the colon, pelvic floor or anorectal apparatus. Based on assessment of colonic transit and anorectal function, patients can be categorized in three groups: normal transit constipation, slow transit constipation and defecatory disorders. Defecatory disorders (DD), also known as obstructed defecation, may coexist with slow transit constipation. The American Gastroenterological Association (AGA) and Rome III criteria both emphasize the need to diagnose DD, because when evacuatory defects are pronounced, soft stools and even enema fluid may be difficult to pass[16].

Obstructed defecation syndrome (ODS) is defined as the inability to defecate properly, despite a normal sensation of the need to do so[13]. This leads to the feeling of incomplete evacuation with long, frequent toilet visits, straining, digitation, and laxative abuse. In most cases of ODS, abnormal morphology of the pelvis, the pelvic floor and the colon and rectum may be present[14]. Although structural abnormalities coexist, the etiology of ODS is incompletely understood and may be conceptualized as maladaptive learning of sphincter contraction[16]. Even the findings of different tests (eg, anal manometry, defecography) may not concur. There is no gold standard for the

diagnosis and traditional treatment approaches (fiber, osmotic or stimulant laxatives and enemas) do not improve the anorectal muscular coordination and may exacerbate the problem.

Biofeedback therapy improves corticoanal function[26] and it alongside of medical management, is the mainstay of treatment of DD. Its main advantages are that it is noninvasive, free of morbidity and with a documented success rate of over 70%[16]. The short-term success rate for biofeedback therapy depends on the patient's motivation, the operator's expertise and skills, and the quality of their interaction with the patient. Successful protocols from tertiary centers have used 5-6 treatment sessions, lasting 30-60 minutes each at two weekly intervals[17]. While the short-term success rates support the use of biofeedback, there is a high failure rate of about 50%-70% at one year. The main drawbacks of biofeedback for ODS are the facts that it is expensive, time-consuming, and it has decreased availability and inconsistent outcomes which are very provider dependent. Because it is delivered in multiple clinic sessions, it is associated with a poorer patient compliance.

There is no current standard of care for patients with refractory defecatory disorders who fail a trial of medication and biofeedback therapy. Options are limited to sacral nerve stimulation, botulinum toxin injection or surgical interventions. Patients who fail, refuse or do not finish biofeedback therapy may be offered botulinum toxin injections into the puborectalis muscle[36]. Sacral nerve stimulation has recently been proven to work for patients with defecatory disorders accompanied by rectal hyposensitivity, but studies are very small, uncontrolled and the response to treatment is inconsistent[27]. Studies assessing the value of partial division of the puborectalis muscle reported mixed results and permanent complications, including incontinence for gas, mucus or feces[29,37]. Total abdominal colectomy with ileorectal anastomosis is the surgical option reserved for patients with chronic constipation who have failed medical therapy. Preliminary studies have shown that it offers significant symptomatic improvement[35], however, like any major surgical procedure, there is a higher risk for complications. An end ileostomy or, if colonic transit is normal, a colostomy are the options of last resort for most patients.

b. Previous clinical studies

Botulinum neurotoxin A is one of the seven neurotoxins produced by C*lostridium botulinum*.[19-20] When injected into the muscle, it binds very specifically to the presynaptic membrane of motoneuron nerve endings and produces chemodenervation that can last for 14 to 16 weeks[21-22]. This long-lasting neuromuscular blockade is achieved through the cleavage of nine amino-acid residues from the carboxyl terminus of synaptosome-associated protein with relative molecular mass 25K (SNAP-25)[24-25]. As a consequence, acetylcholine-containing synaptic vesicles can no longer fuse with the plasma membrane, resulting in the blockade of neurotransmission. The injected muscles become weak over 2-20 days and may recover over 2-4 months as new terminal axons sprout and restore neurotransmission.[23]

Botox was first documented for use in the treatment of anismus in 1988, with a symptomatic improvement in 4 of 7 patients (57%) at 4 weeks after the injection[28]. This was a pilot study and different doses of Botox were used. Two patients developed fecal incontinence that disappeared once the effect of Botox started to fade.

Several phase I and II trials since then demonstrated that Botox is a safe and effective therapeutic approach for ODS[28-35]. There were no severe adverse effects and the overall mortality rate was 0% in all of these studies. Subject to the caveats that the majority of these studies were uncontrolled, with small sample sizes, variable doses, primary outcomes and administration modalities of Botox, their encouraging results led to Botox being increasingly used off-label for patients with pelvic floor disorders who failed medical management and biofeedback therapy. It offers significant advantage in the fact that it can be administered in one session in the office.

Joo et al. [31] injected a dose of Botox contingent with body mass (a total of 12-30 units) in 4 patients with anismus who had failed biofeedback therapy. Symptomatic improvement was noted in all subjects (100%) at 1 and 3 months after the injection. The effect was maintained at one year in 50% of their patients. Shafik and El-Sibai[35] injected 25 IU of Botox in the external anal sphincter of 15 patients with nonrelaxing puborectalis muscle syndrome. Straining at defecation disappeared and stool frequency normalized in 13 of 15 patients (87%) with a mean duration of effect of 4.8 +/- 1.4 SD months. None of the patients treated with Botox reported any adverse effects after the injection.

In 2006, Maria et al. [30] injected 60 IU of Botox in the nonrelaxing puborectalis muscle of 24 patients with chronic outlet obstruction constipation. At 2 months, 19 of 24 patients (79%) had symptomatic improvement. The other five patients who did not respond to the first dose were offered a rescue treatment with 100 IU of Botox. All of them had symptomatic improvement after two months and this improvement persisted to the end of follow-up. At 4 months, 4 of the 19 patients (21%) who initially improved suffered symptomatic recurrence and were successfully retreated with 100 IU of Botox. At an average follow-up of 39+/-17 months, there was no symptomatic recurrence in any of the 24 patients. Two patients (8%) had mild flatus incontinence after the first injection, but there were no other short- or long-term complications or side effects.

Ron et al[32] randomized 25 patients with anismus to receive 20 IU of Botox with two different methods of administration (local injection of Botox-10 units to each side of the puborectalis or 20 units to the posterior aspect of this muscle). Only 29% had a symptomatic improvement in straining index after this dose and the overall satisfaction rate with the treatment was 58%. The reported adverse effects were: 0% incontinence, local infection or bleeding (these remained the same during follow-up after the 1st and 2nd injection). 12.5% of all patients developed mild pain after injection that increased at follow-up.

Faried et al. [29] randomized sixty patients with anismus to receive biofeedback therapy, 100 IU of Botox or posterior division of the puborectalis muscle in. The groups differed significantly in terms of clinical improvement at 1 month (50% for biofeedback, 75% Botox injection, 95% posterior division of the puborectalis muscle, p=0.006). The symptomatic improvement persisted at 1 year in 30% of patients in the biofeedback group, 35% in the Botox group and 70% in the surgery group (p=0.02). No adverse effects were reported for the Botox arm. Two patients in the surgery arm developed incontinence, compared to 0 patients in the Botox and biofeedback arms.

Hompes et al. [36] reported an excellent response of patients with anismus to 100 IU of Botox. Twenty-two (39%) of 56 patients responded initially and 21 ⁄ 22 (95%) underwent repeat injection. At a median follow-up of 19.2 (range, 7.0–30.4) months, 20 ⁄ 21 (95%) had a sustained response and required no further treatment. In 33 (97%) of 34 nonresponders, significant abnormalities were demonstrated at EUA: 31 (94%) had a grade 3–5 rectal prolapse, one had internal anal sphincter myopathy and one had a fissure. Exclusion of these alternative diagnoses revised the initial response rate to 96%. Of 56 patients who received the injection, 4 (7.1%) developed transient minor fecal incontinence (for gas rather than minor soiling). These adverse effects occurred in 4/16 patients who ultimately proved to have rectal prolapse. No Patient with ODS alone had any continence disturbance.

In summary, doses between 50-100 IU of Botox are safe, well tolerated and have been shown in small studies without blinding to provide immediate symptomatic relief in the majority of patients with ODS constipation. For those who did not respond to low doses, higher doses of 100 IU have been used successfully, with improvement in 90-100% of the cases. Based on the available evidence, Botox is a reasonable therapeutic option after failure of conservative management and before more invasive surgery is attempted [34].

c. Rationale behind the proposed research and potential benefits to patients and society

ODS is an undertreated condition, whose prevalence increases with age and is predicted to increase dramatically with the aging population. Botox has been proposed as an effective treatment and it has long been used off-label in ODS patients who refused or failed medical management and biofeedback therapy. However, to this day, no randomized controlled trial has confirmed that Botox is superior to placebo for the treatment of ODS.

We will use 100 IU of Botox, a dose with a good safety profile that has been proven to work in previous studies. We want to evaluate the efficacy of Botox 100 IU compared to placebo in addition to the standard of care (biofeedback therapy) in the treatment of patients diagnosed with ODS. We also plan to document patient compliance with biofeedback therapy.

II. SPECIFIC AIMS

Objective:
To evaluate the efficacy and safety of Botox for the treatment of ODS.

Hypotheses:
Patients treated with Botox will have an improvement in the Altomare Obstructed Defecation Syndrome score (ODS-S) and Patient Assessment of Constipation- Quality of Life Score (PAC-QoL) compared to the placebo group.

III.SUBJECT SELECTION

a. Inclusion/exclusion criteria

Inclusion criteria

- Males and females older than 18 years of all races and backgrounds
- Competent to give informed consent
- Meet the Rome III diagnostic criteria for functional constipation
- Inability to relax the puborectalis muscle at electromyography
- Altomare Obstructed Defecation Syndrome score of 15 points or above
- Failure of treatment with 2 conservative measures which may be as follows:
    - 1 laxative (osmotic or stimulant) for 2 weeks
    - 1 fiber supplement for one month
    - And/or trial of biofeedback for at least 4 sessions

Exclusion criteria

- Previous treatment with botulinum toxin (possible antibodies)
- Known hypersensitivity to any of the components of the toxin
- Presence of allergy or allergic reaction to bupivacaine
- Medication regimen includes narcotics
- Previous radiation therapy to the anal canal and rectum
- Prior proctectomy
- Presence of unhealed and symptomatic anal fissure
- Presence of anal pain
- Presence of fecal incontinence
- Presence of full thickness rectal prolapse
- Presence of internal sphincter myopathy
- Inflammatory bowel disease or proctitis
- Pregnancy or breast-feeding
- Subject is currently enrolled/ just finished participating in a clinical trial in which the intervention/ its carry-over effect may interact with the intervention in this trial

b. Source of subjects and recruitment methods

All patients seen through the Pelvic Floor Disorder Service in colorectal surgery and gastroenterology at MGH who are diagnosed with outlet obstruction will be told about the option to participate in the study by their treating physician/ nurse practitioner.

IV. SUBJECT ENROLLMENT

a. Methods of enrollment

We will enroll 23 patients into the control and 23 patients into the placebo arm of the study. All patients with ODS who are evaluated in the Pelvic Floor Disorders Service at MGH through colorectal surgery and gastroenterology will be informed of the study.

b. Lieba Savitt, N.P. and Holly Milch, NP, initially treats most patients presenting with ODS in our department. Patients with ODS who fail dietary modifications and medical therapy (laxatives and/or biofeedback) are then referred to Liliana Bordeianou, M.D., for discussion of surgical options. In order to avoid the possibility of patients feeling obligated to participate, patients who failed medical management and are interested in participating will initially discuss the study with one of the NPs and have all of their questions answered. Each patient will also receive individualized information about the available treatment options for his/her disease. If still interested, they will be screened based on inclusion and exclusion criteria, and those who qualify will be given the informed consent to take home, read carefully and call back if they wish to participate. Patients who call back will be seen again and allowed to discuss the study in detail with the PI. All further questions will be answered prior to signing consent. If still interested in participation, patients will sign the informed consent with their physician and then schedule their intervention following consent signing.

c. Treatment assignment and randomization

This will be a randomized controlled trial to determine the efficacy of Botox 100 IU compared to placebo for symptom control in adults diagnosed with ODS. Eligible patients who consented to participate are randomized in two groups in a 1:1 ratio to receive either 100 units of Botox or placebo (normal saline) administered under local anesthesia in one office session.

A triple-blinded approach will be used in this study. Subjects, investigators and outcome assessors will be blinded to the group allocation.

Patient treatment group allocation will be done using the method of randomly permuted blocks with random block sizes. This selected type of restricted randomization allows balancing group sizes especially in smaller randomized controlled trials. Subject randomization will be computer generated through the research pharmacy. These results are subsequently kept in the research pharmacy and with the unblinded research nurse who will not interact with the patients

On the day of the procedure, the research nurse will obtain the saline or Botox from the research pharmacy in a brown paper bag. She will then prepare the Botox or draw the normal saline and give it to the investigator for administration. In order to protect blinding, placebo and Botox will have the same characteristics, except for the active drug. The nurse who prepares the drug will also record the study arm in a file kept separate from patient information. Once this is recorded, information will be resealed and kept with patient information until the completion of the study. The nurse who prepared the composition will be the only unblinded member of the healthcare team and will not assist in the procedure.

The adverse effects will be assessed by one standard questionnaire, which allows the description of idiosyncratic reactions and 2 validated questionnaires, which assess the Botox specific adverse effects of fecal incontinence. Outcome measurements and assessment of adverse effects in the office will be made by a research nurse blinded to treatment group allocation.

The PI who delivers the intervention will not take outcome measurements and will have no interaction with the data collectors. The data collectors will be blinded throughout the data entry and data cleaning processes. The statistical analysis will be made after the end of the data collection period. The statistician will only be unblinded once the database is locked. At the end of the study, blinding integrity will be evaluated in a sample of participants and data collectors.

In case of medical emergency, if a study participant has encountered an urgent medical problem and the clinician needs to know his/her intervention group, the allocation code can be broken. Unblinding envelopes (labeled with the randomization number that contains allocation) are sealed by the study center and are only opened if emergency unblinding is necessary.

V. STUDY PROCEDURES

a. Study visits and parameters to be measured

As part of this research study, patients will be asked to come for three visits (Visit 1= return of informed consent and schedule of intervention; Visit 2= intervention; Visit 3=one month after the intervention). They will afterwards be contacted by mail with questionnaires and then with follow-up phone calls (for those who did not return questionnaires) to increase response rate at 3, 6 and 12 months after the intervention.

All patients considered for the study will undergo pretreatment evaluation as per standard of care. This includes a history, clinical examination, and anorectal manometry. Once the patient is deemed eligible to participate, s/he will be offered the opportunity to participate in this trial.

If interested, s/he will meet with the Principal Investigator and/or research nurse practitioner to find out more about this trial. At this time all questions will be answered. Afterwards, s/he will be offered an informed consent form, for review at home. Patients will then be scheduled for a follow-up visit to review and sign consent with PI or study nurse practitioner.

Once all questions are answered and consent is signed, patients will be asked to fill out baseline questionnaires at the visit when consent is signed.

All questionnaires used in this study include validated scores. They will be used to assess the efficacy of the intervention in providing symptomatic improvement and improved quality of life (Altomare ODS score, generic SF-36 version 1, Patient Assessment of Constipation- Quality of Life questionnaire). We will also use 2 standard questionnaires to assess for Botox-specific adverse effects (Cleveland Clinic Fecal Incontinence Score and Fecal Incontinence Quality of Life Scale).

Patients will receive the questionnaires at baseline and then be asked to complete them at their one month follow-up visit.

At one month follow-up visit, patients will meet with their surgeon and the study nurse practitioner. They will first review any adverse reactions which they may have had. Patient will also be asked

about any adverse reactions which will be documented at that visit. They will then undergo anorectal manometry and fill out the questionnaires.

At 3, 6, and 12 months after the injection, patients will be mailed questionnaires. Those participants who do not respond within a month will be contacted by phone to increase response rate.

b. Drugs, devices and surgical procedures to be used

Patients are divided in 2 groups:
Group #1: Placebo

Placebo consists of normal saline and has the same method and route of administration as the active treatment.

Group #2: Botox 100 IU

Each patient in Group #2 will receive a total of 100 units of botulinum toxin, stored in the research phramacy and dispensed to the clinic on the day of the procedure. Botox will be resuspended in 5 ml of sterile saline to a final concentration of 20 U/ml.

For both groups, the interventions will be administered in the office under local anesthesia with 0.25% Marcaine stored in the clinic at 20° to 25°C. We plan to use a 10 mL single dose vial of Marcaine (Bupivacaine Hydrochloride Injection, USP 0.25% (2.5 mg/mL)) administered as local infiltration. More or less drug may be used depending on each individual case. The MGH **Research** Pharmacy will perform the computerized randomization and send up medication or saline in paper bag based on randomization of the subject. Both saline and Botox will be brought from research pharmacy on the day of the procedure in a brown paper bag.

The PI will use transanal ultrasound to clearly identify the puborectalis muscle. Once the muscle is identified, a 23-G needle will be used to inject the agent transanally into the puborectalis and external anal sphincter in three separate locations.

c. Data to be collected

All data are collected prospectively, at the pre-specified time points according to the protocol. All data will be collected in questionnaires attached (see above for specific description). Data from baseline manometry will be taken from patient chart and recorded into REDCap database where data will be stored. Anorectal manometry from 1-month follow-up will also be stored in REDCap database.

VI. BIOSTATISTICAL ANALYSIS

a. Specific data variables being collected for the study

Data collection sheets are attached to this submission. They include the MRN to facilitate data extraction, demographic information (age, sex, race), diagnostic tests at baseline and the study endpoints collected at pre-specified times.

b. Study Endpoints

a) Primary endpoint:

Baseline to 1 month after treatment changes in the sum of Altomare ODS score (ODS-S) and Patient Assessment of Constipation- Quality of Life score (PAC-QoL)

b) Secondary endpoints:

- Baseline to 1, 3, 6 and 12 months after treatment changes in Altomare ODS score (ODS-S) and Patient Assessment of Constipation- Quality of Life score (PAC-QoL)
- Changes in the generic SF-36 version 1, Cleveland Clinic Fecal Incontinence Score (CCFI) and Fecal Incontinence Quality of Life Scale (FIQoL) at 1, 3, 6 and 12 months from baseline
- Relaxation of puborectalis with push measured by EMG at 1 month
- Balloon expulsion test at 1 month
- Manometric changes at 1 month- changes in anal sphincter function (resting sphincter pressure, maximal resting anal pressure, maximum squeeze pressure).
- Change in defecation index [Time Frame: Baseline, 1 month follow-up visit]. The defecation index=maximum rectal pressure during attempted defecation/minimum anal residual pressure during attempted defecation. This is calculated based on measurements obtained from anorectal manometry and is a measure of treatment efficacy.

c. Statistical methods

All analysis will be based on intention-to-treat population in that all randomized subjects will be included in the analysis.

Data will be expressed as mean+/- standard deviation (SD) for all continuous outcomes, and as counts and proportions for all categorical outcomes. The primary analysis (i.e., the comparison of 1-month change in mean ODS-S and PAC-QoL between the 2 treatment arms) will be made by independent samples t-test. Comparison of treatment effect over time (i.e., 1- and 3-, 6- and 12 months) on all scale scores will be performed by using longitudinal linear mixed effects model, which allows to specify the subject specific baseline levels and the time dependent response trajectories (i.e., slopes) random (SAS proc mixed). All p-values are two-tailed and considered significant if $p<0.05$.

d. Power analysis

The proposed sample size is 46 (i.e., 23 in each treatment arm). With an assumption of an attrition rate of up to 15%, we anticipate to attain 40 study completers. The study is designed to detect at

least 25% decrease in mean ODS-S and PAC-QoL at 1 month after treatment with Botox with 80% power at a 5% significance level. This effect size of ≥25% is equivalent to a decrease in mean ODS-S decrease from 15 points at baseline to ≤ 11.4 points at 1 month[37-38].

VII. RISKS AND DISCOMFORTS

a. Complications of surgical and non-surgical procedures

We do not expect any unusual safety concerns in this study. The small foreseeable discomforts and complications will be treated as per standard of care.

b. Drug side effects and toxicities

Botulinum toxin (Botox) has been shown to be very safe and well-tolerated in prior studies, however variable doses of Botox were previously shown to have efficacy. Concerns may arise for potential issues with incontinence for gas, liquid or solid stool if higher doses of Botox are studied. The reported incidence of incontinence has been low in previous studies and it was mostly mild (gas>soiling>solid stool). If incontinence occurs, it may cause significant discomfort to patients who work in a public place and could account for a low recruitment rate and unblinding of patients who experience these adverse effects. Both the active treatment and placebo groups receive transanal injections into three sites. This can cause local discomfort/pain so we will co-administer a long-acting local anesthetic. Patients will also be given instructions to take ibuprofen or acetaminophen as needed for pain relief after procedure. There is the additional risk of infection at the site of injection. The risk of this is low, but all patients will be instructed to call with any symptoms of infection, and will be seen by PI or research nurse practitioner and treated as necessary.

c. Device complications/malfunctions

Not applicable

d. Psychosocial (non-medical) risks

Psychosocial risks may include loss of productivity from appointments. We tried to limit this by administering our surveys via mail and phone and by asking the patients to come in only for the consent, intervention and one visit at 1 month afterwards.

Patients who are in the control group may experience frustration with lack of improvement of their symptoms and frustration from the need to undergo further treatments and investigations at the end of the study. We tried to address this issue by encouraging all patients to receive the standard of care (biofeedback) prior to treatment. Also, at the end of the study, if the medication demonstrates efficacy for ODS, patients in the control group will be offered the option to receive Botox. These patients will be monitored per described plan for this study, but the subjects and investigator will no longer be blinded.

It has been reported that patients enrolled in clinical trials are often frustrated by not knowing the results of their tests and the outcome of the study. To address this, patients will receive a written report of their objective measures (EMG, anorectal manometry, balloon expulsion test) at the one

month visit after the intervention. Also, we will send a letter to each patient when we receive the results, informing him/her of the overall outcome of this study.

e. Radiation Risks

Not applicable

VIII. POTENTIAL BENEFITS

a. Potential benefits to participating individuals

For patients specifically, the potential benefits include an improvement of chronic constipation symptoms and quality of life with a minimally invasive treatment.

b. Potential benefits to society

For society, the potential benefits are great. At this time, few minimally invasive, easily to administer outpatient options for the treatment of ODS are available. The standard of care (biofeedback) is only available in a few select centers across the country and is not a "quick fix" taking multiple sessions to make progress. These may or may not accept the patients' current insurance. On the other hand, the incidence of chronic constipation in the US population is clearly on the rise, as the baby boomers are reaching their 60s. Botox, should it be effective, could alleviate the profound suffering and discomfort associated with this condition. It could also provide an accessible and fast-acting option for the treatment of ODS.

IX. MONITORING AND QUALITY ASSURANCE

a. Independent monitoring of source data

Monthly meetings will be organized to allow monitoring of recruitment of patients, and to assure that the IRB protocols are adhered to. The results of the study will be reviewed at 1/2 of recruitment goals. The study will be halted if a particular study arm appears to be more efficacious or if any unanticipated adverse events occur resulting in serious morbidity or mortality.

b. Safety monitoring

We do not expect any unusual safety concerns in this study as all of the treatments and procedures planned are FDA-approved for a different indication and are thought to be extremely safe.

c. Outcomes monitoring

The principal investigator will monitor completeness of data and assure the validity and integrity of data and adherence to the IRB-approved protocol. She will also review the accuracy and

completeness of case report form entries, source documents and informed consent. IRB will be notified of any major unforeseen complications associated with the study.

d. Adverse event reporting guidelines

Adverse events or other unanticipated problems will be reported to the PHRC as described in the PHRC policy on Adverse Event Reporting and Unanticipated Problems Involving Risks to Subjects or Others, which can be found on the PHRC website:
http://healthcare.partners.org/phsirb/adverse_events.htm
and
http://healthcare.partners.org/phsirb/unantic.htm

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