Document Coversheet

Study Title: Intraoral Administration of Botox in Patients With Dentoalveolar Neuropathic Pain

Institution/Site:	University of Kentucky
Document (Approval/Update) Date:	1/7/2019
NCT Number:	NCT03848143
IRB Number	45231
Coversheet created:	6/15/2026

IRB Approval
1/7/2019
IRB # 45231

PROTOCOL TYPE

Which IRB

◉ Medical ○ NonMedical

Protocol Process Type

○ Exemption
○ Expedited (Must be risk level 1)
◉ Full

IMPORTANT NOTE: Once you have saved your choices under "Which IRB" and "Protocol Process Type", you will not be able to change your selections. If your application is deemed eligible for a different Protocol Process Type, it may be necessary to create a new application.

Please see below for guidance on which selections to make, and/or go to ORI's "Getting Started" web page. If you still have questions about which IRB or Protocol Process Type to choose, please contact the Office of Research Integrity (ORI) at 859-257-9428 prior to saving your selections.

Which IRB

The Medical IRB reviews research emanating from the Colleges of Dentistry; Health Sciences; Medicine; Nursing; Pharmacy and Health Sciences; and Public Health.

The Nonmedical IRBs review research originating from the Colleges of Agriculture; Arts & Sciences; Business & Economics; Communications & Information; Design; Education; Engineering; Fine Arts; Law; and Social Work. The Nonmedical IRB does not review studies that involve administration of drugs or studies that involves invasive medical procedures, regardless of from what college the application originates.

Which Protocol Process Type

Under federal regulations, an investigator's application to conduct a research project involving human subjects can be processed by the IRBs in three ways:

- by full review;
- by exemption certification;
- by expedited review.

The preliminary determination that a research project is eligible for exemption certification or expedited review is made by the investigator. For assistance in determining which review process type your IRB application is eligible for, please go to ORI's "Getting Started" web page.

The revised Common Rule expanded exemption certification category 4 for certain secondary research with identifiable information or biospecimens. The regulations no longer require the information or biospecimens to be existing. For more information see the Exemption Categories Tool.

PROJECT INFORMATION

Title of Project: (If applicable, use the exact title listed in the grant/contract application).

Intraoral administration of onabotulinum toxin A for continuous neuropathic pain: a single subject experimental design

Short Title Description

Note: "Short Title" should consist of a couple key words to easily identify your study - these key words (rather than the whole title) will be displayed on the Dashboard in the listing for your study.

Botox neuropathic pain

Anticipated Ending Date of Research Project: 12/31/2019

Number of human subjects: 50

Study is/will be open to new subject enrollment (or data/specimen collection): (•) Yes ( ) No

PI CONTACT INFORMATION

The Principal Investigator's (PI) contact information is filled in automatically based on who was logged in when the application was created (with LinkBlue ID). If research is being submitted to or supported by an extramural funding agency such as NIH, a private foundation or a pharmaceutical/manufacturing company, the PI listed on the grant application or the drug protocol must be the same person listed below.

If you are not the Principal Investigator, do NOT add yourself as study personnel. You may change the PI contact information on an application that is in Researcher edit mode by:

- clicking the "Change Principal Investigator" link below;
- searching for the PI's name using the search feature;
- clicking "Select" by the name of the Principal Investigator, then "Save Contact Information".

You will automatically be added as study personnel with edit authorization so you can continue editing the application.

Please fill in any blank fields with the appropriate contact information (gray shaded fields are not editable). Required fields left blank will be highlighted in pink after you click "Save".

To change home and work addresses, go to myUK and update using the Employee Self Service (ESS) portal. If name has changed, the individual with the name change will need to submit a 'Name Change Form' to the Human Resources Benefits Office for entering into SAP. The new name will need to be associated with the individual's Link Blue ID in SAP before the change is reflected in E-IRB. Contact the HR Benefits Office for additional information.

Note: Principal Investigator (PI) role for E-IRB access
The PI is the individual holding primary responsibility on the research project with the following permissions on the E-IRB application:

1. Read;
2. write/edit;
3. receive communications; and
4. submit to the IRB (IR, CR, MR, Other Review*).

Change Principal Investigator:

First Name:	Isabel	Room# & Bldg:	OFP
Last Name:	Moreno Hay	Speed Sort#:	40536
Middle Name			
Department:	Dentistry Oral Health Science …	Dept Code:	7A800
PI's Employee/Student ID#:	10752795	Rank:	
PI's Telephone #:	8593233440	Degree:	DDS PhD
PI's e-mail address:	imo226@uky.edu	PI's FAX Number:	8593230001
PI is R.N.	○ Yes ◉ No	Trained:	Yes
		Date Trained	2/26/2016

Do you, the PI, have a significant financial interest related to your responsibilities at the University of Kentucky (that requires disclosure per the UK administrative regulation 7:2)?

○ Yes ◉ No

RISK LEVEL

Indicate which of the categories listed below accurately describes this protocol

- ○ (Risk Level 1) Not greater than minimal risk
- ◉ (Risk Level 2) Greater than minimal risk, but presenting the prospect of direct benefit to individuals subjects
- ○ (Risk Level 3) Greater then minimal risk, no prospect of direct benefit to individual subjects, but likely to yield generalizable knowledge about the subject's disorder or condition.
- ○ (Risk Level 4) Research not otherwise approvable which presents an opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare of subjects.

*"Minimal risk" means that the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves from those ordinarily encountered in daily life or during the performance of routine physical or psychological examination or tests [45 CFR 46.102(i)]

Download UK's guidance document on assessing the research risk for additional information on risk [PDF]

SUBJECT DEMOGRAPHICS

Age level of human subjects: (i.e., 6 mths.; 2yrs., etc..) 18 to 90

Indicate the targeted/planned enrollment of the following members of minority groups and their subpopulations
(Please note: The IRB will expect this information to be reported at Continuation Review time):

Enter Numbers Only!

Ethnic Origin	#Male	#Female
American Indian/Alaskan Native:	0	0
Asian:	1	1
Black African American:	3	3
Hispanic/Latino:	2	2
Native Hawaiian/Pacific Islander:	0	0
White/Caucasian:	20	20
Other or Unknown:		

If unknown, please explain why:

Indicate the categories of subjects and controls to be included in the study. Depending on the subject category applicable to your research you may be required to complete additional forms. [Note, if the study does not involve direct intervention or direct interaction with subjects, (e.g., record-review research, outcomes registries), do not check mark populations which the research does not specifically target. For instance, a large record review of a diverse population may incidentally include a prisoner or an international citizen, but, if the focus or intent of the study has nothing to do with that status, you do not need to check those category(ies).]

Check All That Apply (at least one item must be selected)

- ☐ Children (individuals under age 18)
- ☐ Wards of the State (Children)
- ☐ Emancipated Minors
- ☐ Students
- ☐ College of Medicine Students
- ☐ UK Medical Center Residents or House Officers
- ☐ Impaired Consent Capacity Adults
- ☐ Pregnant Women/Neonates/Fetal

ADDITIONAL INFORMATION:

Please visit the IRB Survival Handbook under the named topic:

- Children/Emancipated Minors
- Students as Subjects
- Prisoners
- Impaired Consent Capacity Adults: Link to required Form

And/Or:

- UKMC Residents or House Officers [see requirement of GME]

Material

- ☐ Prisoners
- ☐ Non-English Speaking
- ☐ International Citizens
- ☐ Normal Volunteers
- ☐ Military Personnel and/or DoD Civilian Employees
- ☑ Patients
- ☐ Appalachian Population

- Non-English Speaking [see instructions for recruitment and E-IRB Research Description section on same topic]
- International Citizens [HTML] (DoD SOP may apply [PDF])
- Military Personnel and/or DoD Civilian Employees (DoD SOP may apply [PDF])

The next questions involve assessment of the study relative to potential recruitment of subjects with impaired consent capacity (or likelihood).

☐ Check this box if your study does not involve direct intervention or direct interaction with subjects (e.g., record-review research, secondary data analysis). (you will not need to answer the impaired consent capacity questions)

Does this study focus on adult subjects with any of the clinical conditions listed below that present a high *likelihood* of impaired consent capacity or *fluctuations* in consent capacity? (see examples below)

◉ Yes ○ No

If Yes, go to the following link and complete and attach the indicated form unless you are filing for an exemption certification: https://ris.uky.edu/ori/oriforms/formt/Scale.asp

Examples of such conditions include:

- Traumatic brain injury or acquired brain injury
- Severe depressive disorders or Bipolar disorders
- Schizophrenia or other mental disorders that involve serious cognitive disturbances
- Stroke
- Developmental disabilities
- Degenerative dementias
- CNS cancers and other cancers with possible CNS involvement
- Late stage Parkinson's Disease
- Late stage persistent substance dependence
- Ischemic heart disease
- HIV/AIDS
- COPD
- Renal insufficiency
- Diabetes
- Autoimmune or inflammatory disorders
- Chronic non-malignant pain disorders
- Drug effects
- Other acute medical crises

Attachments

Attach Type	File Name
ImpairedConsent	Form_T_2Ai (1).doc

INFORMED CONSENT/ASSENT PROCESS/WAIVER

For your informed consent attachment(s), please download the most up-to-date version listed in "All Templates" under the APPLICATION LINKS menu on the left, and revise to be in accord with your research project.

Additional Resources:

- Sample Repository/Registry/Bank Consent (PDF) (Word)
- Instructions for Proposed Informed Consent Document
- Instructions for Proposed Assent Form

Consent/Assent Tips:

- **If you have multiple consent documents, be sure to upload each individually (not all in a combined file).**
- **Changes to consent documents (e.g., informed consent form, assent form, cover letter, etc...) should be reflected in a 'tracked changes' version and uploaded separately with the Document Type "Highlighted Changes".**
- **It is very important that only the documents you wish to have approved by the IRB are attached; DELETE OUTDATED FILES -- previously *approved* versions will still be available in Protocol History.**
- **Attachments that are assigned a Document Type to which an IRB approval stamp applies will be considered the version(s) to be used for enrolling subjects once IRB approval has been issued.**
  Document Types that do NOT get an IRB approval stamp are:
  - **"Highlighted Changes",**
  - **"Phone Script", and**
  - **"Sponsor's Sample Consent Form".**

How to Get the Informed Consent Section Check Mark

1. **You must check the box for at least one of the consent items and/or check mark one of the waivers, then if applicable attach the corresponding document(s) as a PDF (if open to enrollment).**
2. **If you no longer need a consent document approved (e.g., closed to enrollment), or, the consent document submitted does not need a stamp for enrolling subjects (e.g., umbrella study, or sub-study), only check mark the "Stamped Consent Doc(s) Not Needed".**
3. **After making your selection(s) be sure to scroll to the bottom of this section and SAVE your work!**

Check All That Apply

- ☑ Informed Consent Form (and/or Parental Permission Form)
- ☐ Assent Form
- ☐ Cover Letter (for survey/questionnaire research)
- ☐ Phone Script
- ☐ Informed Consent/HIPAA Combined Form
- ☐ Debriefing and/or Permission to Use Data Form
- ☐ Sponsor's sample consent form for Dept. of Health and Human Services (DHHS)-approved protocol
- ☐ Stamped Consent Doc(s) Not Needed

Attachments

☐ Request for Waiver of Informed Consent Process

If you are requesting IRB approval for waiver of the requirement for the informed consent process, or alteration of some or all of the elements of informed consent (i.e. medical record review, deception research, or collection of biological specimens), complete Section 1 and Section 2 below.

Note: The IRB does not approve waiver or alteration of the consent process for greater than minimal risk research, except for planned emergency/acute care research as provided under FDA regulations. Contact ORI for regulations that apply to single emergency use waiver or acute care research waiver (859-257-9428).

SECTION 1.

Check the appropriate item:

☐ I am requesting waiver of the requirement for the informed consent process.

☐ I am requesting alteration of the informed consent process.

If you checked the box for this item, describe which elements of consent will be altered, and/or omitted, and justify the alteration.

SECTION 2.

The IRB may consider your request provided that **all** of the following conditions apply to your research and are appropriately justified. Explain in the space provided for each condition how it applies to your research.

a) The research involves no more than minimal risk to the subject.

b) The rights and welfare of subjects will not be adversely affected.

c) The research could not practicably be carried out without the requested waiver or alteration.

d) Whenever possible, the subjects or legally authorized representatives will be provided with additional pertinent information after they have participated in the study.

Request for Waiver of Documentation of Informed Consent Process

If you are requesting IRB approval for waiver of the requirement for documentation of informed consent (i.e. telephone survey or mailed survey, internet research, or certain international research), **your research activities must fit into one of three regulatory options**:

1. The only record linking the participant and the research would be the consent document, and the principal risk would be potential harm resulting from a breach of confidentiality (i.e., a study that involves participants who use illegal drugs).
2. The research presents no more than minimal risk to the participant and involves no procedures for which written consent is normally required outside of the research context (i.e. a cover letter on a survey, or a phone script).
3. The participant (or legally authorized representative) is a member of a distinct cultural group or community in which signing forms is not the norm, and the research presents no more than minimal risk to the subject and there is an appropriate alternative mechanism for documenting that informed consent was obtained.

Select the option below that best fits your study, and explain in the space provided how your study meets the criteria for the selected regulatory option.

Note: The IRB cannot waive the requirement for documentation or alter the consent form for FDA-regulated research unless it meets Option #2 below. FDA does not accept Option #1.

Note: Even if a waiver of the requirement for documentation is approved by the IRB, participants must still be provided oral or written (e.g., cover letter) information including all required and appropriate elements of consent so they have the knowledge and opportunity to consider whether or not to participate. To help ensure required elements are included in your consent document, please use the **Cover Letter Template** as a guide: *English*- [WORD], Spanish- [WORD] The cover letter template was developed specifically for survey/questionnaire research; however, it may be useful as a guide for developing a consent document for other types of research as well.

Option 1

a) The only record linking the participant and the research would be the consent document:

b) The principal risk would be potential harm resulting from a breach of confidentiality (i.e., a study that involves subjects who use illegal drugs).

Under this option, each participant (or legally authorized representative) must be asked whether (s)he wants to sign a consent document; if the participant agrees to sign a consent document, only an IRB approved version should be used.

Option 2

a) The research presents no more than minimal risk to the participant:

b) Involves no procedures for which written consent is normally required outside of the research context (i.e. a cover letter on a survey, or a phone script):

Option 3

a) The subject (or legally authorized representative) is a member of a distinct cultural group or community in which signing forms is not the norm.

b) The research presents no more than minimal risk to the subject.

c) There is an appropriate alternative mechanism for documenting that informed consent was obtained.

STUDY PERSONNEL

Do you have study personnel who will be assisting with the research?
After selecting 'Yes' or 'No' you must save by hitting the 'Save Study Personnel Information' button.

◉ Yes ○ No

Manage Study Personnel

Identify other study personnel assisting in research project:

- The individual listed as PI in the 'PI Contact Information' section should NOT be added to this section.
- If the research is being completed to meet the requirements of a University of Kentucky academic program, the faculty advisor is also considered study personnel and should be listed as such below.
- Role: DP = Editor (individual can view, navigate, and edit the application for any review phase (IR, CR, MR) or 'Other Review", and submit Other Reviews on behalf of the PI.)
- Role: SP = Reader (individual can view and navigate through the currently approved application only.)

To add an individual via the below feature, search for applicable personnel first, then click "select" by the listing for the person you want to add as study personnel to your protocol. For each individual selected, be sure to specify responsibility in the project, whether authorized by the principal investigator to obtain informed consent, AND denote who should regularly receive E-IRB notifications.

NOTE: Study personnel are required to receive human research protection (HSP) training before implementing any research procedures (e.g., CITI). For information about mandatory training requirements for study personnel, visit UK's FAQ's on Mandatory Training web page, or contact ORI at 859-257-9428. If you have documentation of current HSP training other than that acquired through UK CITI, you may submit it to ORI (Jen.Hill@uky.edu) for credit.

Study personnel assisting in research project:

Add Personnel

My Study Personnel	Last Name	First Name	Responsibility In Project	Role	AC	Contact	Degree	StatusFlag	(HSP)	(HSP)Date	Removed?	Last Updated	Recorded Training	SFI
Details	Carlson	Charles	Faculty Advisor	DP	N	N	PhD	P	Y	11/07/2016	N	09/04/2018	00001601	N
Details	Okeson	Jeffrey	Co-Investigator	DP	Y	N	DMD	P	Y	07/10/2017	N	08/30/2018	00004971	N

RESEARCH DESCRIPTION

****!!!PLEASE READ!!!** Known Issue: The below text boxes do not allow symbols, web addresses, or special characters (characters on a standard keyboard should be ok). If something is entered that the text boxes don't allow, user will lose unsaved information.**

Workaround(s):

- **Save your work often to avoid losing data.**
- **Use one of the attachment buttons in this section, or under the Additional Information section to include the information with your application. During the document upload process, you will be able to provide a brief description of the attachment.**

Background: Provide an introduction and background information. Describe past experimental and/or clinical findings leading to the formulation of your study. For research involving investigational drugs, describe the previously conducted animal and human studies. You may reference grant application/sponsor's relevant protocol pages and attach as an appendix in the E-IRB "Additional Information" section. For research that involves FDA approved drugs or devices, describe the FDA approved uses of this drug/device in relation to your protocol. Attach a copy of the approved labeling as a product package insert or from the Physician's Desk Reference in the applicable E-IRB "Study Drug" or "Study Device" section.

Onabotulinum toxin type A (BoNT-A) is a potent neurotoxin produced by the anaerobic bacteria Clostridium botulinum and other Clostridum species. The toxin blocks the release of acetylcholine (ACh) from the presynaptic efferent (motor) nerve endings. More recently, BoNT-A has also been reported to have an effect on afferent (sensory) neurons independent of its action on muscle tone and secretory glands at the periphery. In animal models, BoNT-A has been shown to have an effect on the accumulation of presynaptic CGRP of afferent neurons inhibiting the peptide exocytosis, thus, potentially alleviating pain (1). The peripheral and intrathecal administration of BoNT-A in formalin-induced pain models also decreased the intensity of pain (2, 3). In a capsaicin inflammatory pain model, the infiltration of BoNT-A previous to the induction of the inflammation prevented mechanical and thermal hyperalgesia (4). Additionally, in neuropathic pain models, the administration of peripheral and intrathecal BoNT-A reduced mechanical and thermal hyperalgesia (5-9). These findings suggest that BoNT-A acts not only in the periphery but also reduces central sensitization. In human studies, the use of BoNT-A has proven to reduce the severity and intensity of attacks in chronic tension type headaches (10) and chronic neck pain (11). The PREEMPT study concluded that BoNT-A could be used as a preventive therapy in chronic migraine patients (12) and FDA approval was obtained. According to the revised systematic review and metanalysis funded by the Special Interest Group on Neuropathic Pain (NeuPSIG) of the International Association for the Study of Pain (IASP), BoNT-A is recommended for peripheral neuropathic pain with moderate quality evidence (only 6 RCTs are available to assess the efficacy of BoNT-A). Subcutaneous administration of 50-200U to onabotulinum toxin A to the painful neuropathic area, repeated every 3 months, is recommended by the IASP guidelines as a third line of treatment. The number needed to treat was 1.9 in four of the smaller studies and the reported drug safety was good (13). To our knowledge, there are no clinical trials published investigating the effect of intraoral administration of BoNT-A in continuous dentoalveolar neuropathic pain. REFERENCES 1. Dolly J.O., O'Connell M.A. Neurotherapeutics to inhibit exocytosis from sensory neurons for the control of chronic pain. Current opinion in pharmacology. 2012;12(1):100-8. 2. Cui M., Khanijou S., Rubino J., Aoki K.R. Subcutaneous administration of botulinum toxin A reduces formalin-induced pain. Pain. 2004;107(1-2):125-33. 3. Luvisetto S., Marinelli S., Lucchetti F., Marchi F., Cobianchi S., Rossetto O., et al. Botulinum neurotoxins and formalin-induced pain: central vs. peripheral effects in mice. Brain research. 2006;1082(1):124-31. 4. Bach-Rojecky L., Lackovic Z. Antinociceptive effect of botulinum toxin type a in rat model of carrageenan and capsaicin induced pain. Croatian medical journal. 2005;46(2):201-8. 5. Marinelli S., Luvisetto S., Cobianchi S., Makuch W., Obara I., Mezzaroma E., et al. Botulinum neurotoxin type A counteracts neuropathic pain and facilitates functional recovery after peripheral nerve injury in animal models. Neuroscience. 2010;171(1):316-28. 6. Bach-Rojecky L., Relja M., Lackovic Z. Botulinum toxin type A in experimental neuropathic pain. Journal of neural transmission. 2005;112(2):215-9. 7. Park H.J., Lee Y., Lee J., Park C., Moon D.E. The effects of botulinum toxin A on mechanical and cold allodynia in a rat model of neuropathic pain. Canadian journal of anaesthesia = Journal canadien d'anesthesie. 2006;53(5):470-7. 8. Bach-Rojecky L., Salkovic-Petrisic M., Lackovic Z. Botulinum toxin type A reduces pain supersensitivity in experimental diabetic neuropathy: bilateral effect after unilateral injection. European journal of pharmacology. 2010;633(1-3):10-4. 9. Filipovic B., Bach-Rojecky L., Lackovic Z. Lasting reduction of postsurgical hyperalgesia after single injection of botulinum toxin type A in rat. Fundamental & clinical pharmacology. 2010;24(1):43-5. 10. Relja M., Telarovic S. Botulinum toxin in tension-type headache. Journal of neurology. 2004;251 Suppl 1:I12-4. 11. Miller D., Richardson D., Eisa M., Bajwa R.J., Jabbari B. Botulinum neurotoxin-A for treatment of refractory neck pain: a randomized, double-blind study. Pain medicine. 2009;10(6):1012-7. 12. Dodick D.W., Turkel C.C., DeGryse R.E., Aurora S.K., Silberstein S.D., Lipton R.B., et al. OnabotulinumtoxinA for treatment of chronic migraine: pooled results from the double-blind, randomized, placebo-controlled phases of the PREEMPT clinical program. Headache. 2010;50(6):921-36. 13. Finnerup N.B., Attal N., Haroutounian S., McNicol E., Baron R., Dworkin R.H., et al. Pharmacotherapy for neuropathic pain in adults: a systematic review and meta-analysis. The Lancet Neurology. 2015;14(2):162-73. 14. Barlow DH, Hersen, H.M. Single case experimental design. 1st ed: New York: Pergamon Press; 1976.

Objectives: List your research objectives. You may reference grant application/sponsor's relevant protocol pages and attach as an appendix in the E-IRB "Additional Information" section.

PRIMARY OBJECTIVES: 1. Determine if the intraoral infiltration of onabotulinum toxin type A (BoNT-A) to the painful area can provide a therapeutic benefit in subjects suffering from continuous dentoalveolar neuropathic pain. 2. Determine the latency period of the therapeutic effect after the intraoral infiltration of BoNT-A to the painful area in subjects suffering from continuous dentoalveolar neuropathic pain. 3. Determine the duration of the therapeutic effect of the intraoral infiltration of BoNT-A in subjects suffering from

continuous dentoalveolar neuropathic pain. SECONDARY OBJECTIVES: 1. Assess the safety and adverse effects of intraoral infiltration of BoNT-A.

Study Design: Describe the study design (e.g., single/double blind, parallel, crossover, etc.). Indicate whether or not the subjects will receive placebo medication at some point in the research procedures. Also, indicate whether or not the subjects will be randomized in this study. You may reference sponsor's protocol pages and attach as an appendix in the E-IRB "Additional Information" section. (Including the study design table from a sponsor's protocol is helpful to IRB members.)

Community-Based Participatory Research: If you are conducting community-based participatory research (CBPR), describe strategies for involvement of community members in the design and implementation of the study, and dissemination of results from the study.

Research Repositories: If the purpose of this submission is to establish a Research Repository (bank, registry) indicate whether the material you plan to collect would or would not be available from a commercial supplier, clinical lab, or established IRB approved research repository. Provide scientific justification for establishment of an additional repository collecting duplicate material. Describe the repository design and operating procedures. For relevant information to include, see the UK Research Biospecimen Bank Guidance [PDF] or the UK Research Registry Guidance [PDF]

Single Subject Experimental Study

Attachments

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Study Population: Describe the characteristics of the subject population, such as anticipated number, age range, gender, ethnic background and health status. Identify the criteria for inclusion and exclusion. Explain the rationale for the use of special classes such as fetuses, pregnant women, children, institutionalized, adults with impaired consent capacity, prisoners, economically or educationally disadvantaged persons or others who are likely to be vulnerable.

If women or minorities are included, please address how the inclusion of women and members of minority groups and their subpopulations will help you meet your scientific objectives. Exclusion of women or minorities requires clear and compelling rationale that shows inclusion is inappropriate with respect to the health of the subjects or that inclusion is inappropriate for the purpose of the study. Cost is not an acceptable reason for exclusion except when the study would duplicate data from other sources. Women of childbearing potential should not be excluded routinely from participation in clinical research.

Provide the following information:

- A description of the subject selection criteria and rationale for selection in terms of the scientific objectives and proposed study design;
- A compelling rationale for proposed exclusion of any sex/gender or racial/ethnic group;
- The proposed dates of enrollment (beginning and end);
- The proposed sample composition of subjects.

You may reference grant application/sponsor's relevant protocol pages and attach as an appendix using the below attachment button.

In this study, subjects will be recruited from a patient population seeking care for continuous dentoalveolar neuropathic pain at the Orofacial Pain Center (University of Kentucky). The inclusion criteria include: 1. Older than 18 years old. 2. History of continuous dentoalveolar pain with clinically evident positive (hyperalgesia, allodynia) and/or negative (hypoaesthesia, hypoalgesia) signs of trigeminal nerve dysfunction and where other possible pain sources have been ruled out. 3. Intractable pain to conventional oral and/or topical pharmacotherapy for neuropathic pain according to the recommendations published by NeuPSIG (13) including: anticonvulsants, SNRIs and/or tricyclic antidepressants. 4. Subject consent to participate in the study. The exclusion criteria include: hypersensitive to any onabotulinum toxin preparation or any component in the formulation, systemic nerve or muscle disorders, bleeding disorders, dysphagia, breathing problems, pregnancy or breastfeeding and previous treatment with botulinum toxin in the last 4 months.

Attachments

Subject Recruitment Methods & Privacy: Using active voice, describe plans for the identification and recruitment of subjects, including how the population will be identified, and how initial contact will be made with potential subjects by those having legitimate access to the subjects' identity and the subjects' information.

Describe the setting in which an individual will be interacting with an investigator or how and where members of the research team will meet potential participants. If applicable, describe proposed outreach programs for recruiting women, minorities, or disparate populations as participants in clinical research. Describe steps taken to minimize undue influence in recruiting potential participants.

Please note: Based upon both legal and ethical concerns, the UK IRB does not approve finder's fees or "cold call" procedures made by research staff unknown to the potential participant.

For additional details, see topic "Recruitment of Subjects/Advertising" on ORI's IRB Survival Handbook web page and the PI Guide to

Identification and Recruitment of Human Subjects for Research [PDF].

Subjects will be recruited among the patients treated at the Orofacial Pain Center. Our medical providers at the Orofacial Pain Center, provide diagnosis and management for a variety of orofacial pain conditions, including neuropathic pain. If patients have been previously diagnosed with dentoalveolar continuous neuropathic pain, meet the inclusion criteria for our study, they will then be invited to participate in our study.

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Advertising: Specify if any advertising will be performed. If yes, please see "IRB Application Instructions - Advertisements" for instructions on attaching copies of the information to be used in flyers or advertisements. Advertisements must be reviewed and approved by the IRB prior to use. For additional details, see topic "Recruitment of Subjects/Advertising" on ORI's IRB Survival Handbook web page for the *PI Guide to Identification and Recruitment of Human Subjects for Research* [D7.0000] document [PDF]. If you will be recruiting subjects via advertising at non-UK owned or operated sites, you should include a copy of written permission from that site to place the advertisement in their facilities.

Note: Print and media advertisements that will be presented to the public also require review by UK Public Relations (PR) to ensure compliance with UK graphic standards, and equal opportunity language.

No advertising will be performed

Attachments

Informed Consent Process: Using active voice, describe the consent/assent procedures to be followed, the circumstances under which consent will be sought and obtained, the timing of obtaining informed consent, whether there is any waiting period between informing the prospective subject and obtaining consent, who will seek consent., steps taken to minimize the possibility of coercion or undue influence, the method used for documenting consent, and if applicable who is authorized to provide permission or consent on behalf of the subject. Note: all individuals authorized to obtain informed consent should be designated as such in the E-IRB "Study Personnel" section of this application.

Describe provisions for obtaining consent/assent among any relevant special populations such as children (see Children in Research Policy [PDF] for guidance), prisoners (see Summary of Prisoner Regulations [PDF] for guidance), and persons with impaired decisional capacity (see Impaired Consent Capacity Policy [PDF] for guidance). Describe, if applicable, use of specific instruments or techniques to assess and confirm potential subjects' understanding of the nature of the elements of informed consent and/or a description of other written materials that will be provided to participants or legally authorized representatives. If you have a script, please prepare it using the informed consent template as a guide, and submit it on a separate page.

Informed Consent for Research Involving Emancipated Individuals
If you plan to enroll some or all prospective subjects as emancipated, consult with UK legal counsel **when preparing the IRB application and prior to submitting the application to the IRB**. Include legal counsel's recommendations (legal counsel's recommendations may be attached in the E-IRB "Additional Information" section as a separate document, if necessary). For a complete definition of emancipated minors, see the section on *Emancipated Individuals* in the Informed Consent SOP [PDF].

Informed Consent for Research Involving Non-English Speaking Subjects
If you are recruiting non-English speaking subjects, the method by which consent is obtained should be in language in which the subject is proficient. Describe the process for obtaining informed consent from prospective subjects in their respective language (or the legally authorized representative's respective language). In order to ensure that individuals are appropriately informed about the study when English is their second-language, describe a plan for evaluating the level of English comprehension, and the threshold for providing a translation, or explain why an evaluation would not be necessary. For additional information on inclusion of non-English speaking subjects, or subjects from a foreign culture, see IRB Application Instructions for Recruiting Non-English Speaking Participants or Participants from a Foreign Culture.

Research Repositories
If the purpose of this submission is to establish a research repository describe the informed consent process. For guidance regarding consent issues, process approaches, and sample language see the Sample Repository/Registry/Bank Consent Template [PDF]

Informed consent will be obtained for each potential participant according to the inclusion and exclusion criteria of the study. Two copies of the informed consent form will be provided to each participant. Patients will be informed that if they decline to participate in the study it will not influence their treatment at the Orofacial Pain Center, and that they can decline their participation at any time during the study. Any concerns or questions that the potential participants might have will be answered and discussed by the study personnel. Once patients have decided to participate in the study, they will return the informed consent form dated and signed. A copy of informed consent form will be provided to the participant.

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Research Procedures: Describe the research procedures that will be followed. Identify all procedures that will be carried out with each group of subjects. Differentiate between procedures that involve standard/routine clinical care and those that will be performed specifically for this research project.

After consent form is obtained, patients will be provided with instructions on how to complete daily pain surveys during the length of the study (7 months total). These pain surveys can either be completed via a link that will be mailed to the patient or thought a written pain questionnaire. After one month of data collection about the pain levels at baseline, patient will return to the Orofacial Pain Clinic to receive 50 U of BoNT-A constituted in 1 mL of saline solution injected intraorally to the painful area. Dependin on the size of the affected area the infiltration might be divided in 3 injection sites, 0.5 to 1.0 cm apart following a checkerboard pattern. Photographs of the injection sites marked intraorally will be taken to record the anatomical location. A phone call will be made to the patient one week after the injection to discuss any adverse effects and, if indicated, the patient will be asked to return for a clinical evaluation at the Orofacial Pain Clinic. 3 months after the first infiltration, subjects will be rescheduled to repeat the infiltration following the same protocol as described above. Photographs will be used to determine the injection sites. One week after the second infiltration, a follow up will be performed over the phone to identify any potential adverse effects. During the length of the study patients will be asked to complete a daily pain survey with the same questions about pain levels, and side effects. Three months after the second infiltration, those patients who would have completed the pain survey through a written document would be asked to return them via mail or hand delivered to the clinic.

Attachments

Data Collection: List the data or attach a list of the data to be collected about or from each subject (e.g. interview script, survey tool, data collection form for existing data).

If the research includes survey or interview procedures, the questionnaire, interview questions or assessment scales should be included in the application (use attachment button below).

The data collection instrument(s) can be submitted with your application in draft form with the understanding that the final copy will be

submitted to the IRB for approval prior to use (submit final version to the IRB for review as a modification request if initial IRB approval was issued while the data collection instrument was in draft form).

Subjects will be recruited among the patients diagnosed with dentoalveolar continuous neuropathic pain at the Orofacial Pain Center. Patient's chart will be reviewed to collect the following data: demographics including: gender, age, occupation, and marital status. Disease diagnosis and information from the clinical examination such as location of pain, presence of sensory deficits, and response to application of local anesthetic. Results from the psychological and pain questionnaires completed by the patient at their initial evaluation (see attachments). These data will be collected from the patient's chart as part of the standard of care. In addition, results from the pain surveys will be collected as part of the research project, as well as the information collected from follow up phone interview.

Attachments

Attach Type	File Name
DataCollection	Daily_pain_diary.pdf
DataCollection	Pain Follow Up Questionnaire_phone.pdf
DataCollection	Pain New Patient Questionnaire Jul 2018.pdf
DataCollection	Psych_package_August_2018.pdf

Resources: Describe what resources/facilities are available to perform the research (i.e., staff, space, equipment). Such resources may include a) staffing and personnel, in terms of availability, number, expertise, and experience; b) psychological, social, or medical services, including counseling or social support services that may be required because of research participation; c) psychological, social, or medical monitoring, ancillary care, equipment needed to protect subjects; d) resources for subject communication, such as language translation services, and e) computer or other technological resources, mobile or otherwise, required or created during the conduct of the research. Please note: Some mobile apps may be considered mobile medical devices under FDA regulations (see FDA Guidance). Proximity or availability of other resources should also be taken into consideration, for example, the proximity of an emergency facility for care of subject injury, or availability of psychological support after participation.

Research activities conducted at performance sites that are not owned or operated by the University of Kentucky, at sites that are geographically separate from UK, or at sites that do not fall under the UK IRB's authority, are subject to special procedures for coordination of research review. Additional information is required (see IRB Application Instructions - Off-Site Research web page); supportive documentation can be attached in the E-IRB "Additional Information" section. Provide a written description of the role of the non-UK site(s) or non-UK personnel who will be participating in your research. The other site may need to complete its own IRB review, or a cooperative review arrangement may need to be established. Contact the Office of Research Integrity at (859) 257-9428 if you have questions about the participation of non-UK sites/personnel.

If the University of Kentucky is the lead site in a multi-site study, or the UK investigator is the lead investigator, describe the plan for managing the reporting of unanticipated problems, noncompliance and submission of protocol modifications and interim results from the non-UK sites.

The study will be conducted within the facilities of the Orofacial Pain Center. The clinic is equipped with all the material necessary to perform the procedures and Allergan, Inc will be providing the drug that will be delivered. The medication will be kept in a refrigerator locked inside of the laboratory of the Orofacial Pain Center. Room E239. The clinical examination and procedure will be performed by the study personnel involved in this research: Dr. Isabel Moreno Hay, DDS PhD and Dr. Jeffrey P. Okeson, DMD. All of the members of the research team have extensive experience in research at the University of Kentucky. They are all compliant with the CITI certification.

Potential Risks: Describe any potential risks or likely adverse effects of the drugs, biologics, devices or procedures subjects may encounter while in the study. Please describe any physical, psychological, social, legal or other risks and assess their likelihood and seriousness.

The risks or complications that can be associated with the injection of onabotulinum toxin A (BOTOX®) include: Adverse effects that usually occur in 1 week and may last up to several months: • Frequent (>10%): Headaches (11%), dysphagia (19%), neck pain (11%), upper respiratory tract infection (12%), • Occasional (2-10%): Dizziness (2-10%), hypertonia (2-10%), numbness (2-10%), speech disturbances (2-10%), drowsiness, nausea (2-10%), xerostomia (2-10%), antibody development (1%), injection site soreness (2-10%), stiffness (2-10%), asthenia (2-10%), blepharoptosis (2-10%), diplopia (2-10%), cough (2-10%), dyspnea (2-10%), flu-like symptoms (2-10%), rhinitis (2-10%), fever (2-10%), hypertension (2%), exacerbation of migraine headache (4%), facial paresis (2%), myasthenia (4%), musculoskeletal pain (3%), myalgia (3%), muscle spasm (2%) • Rare (<1%): abdominal pain, alopecia, amyotrophy, anaphylaxis, anorexia, antibody development (neutralizing), aspiration pneumonia, asthma, blurred vision, brachial plexopathy, cardiac arrhythmia, corneal perforation, corneal ulceration, denervation, dermatitis, diarrhea, drug toxicity (botulinum toxin effects), dry eye syndrome, dysarthria, erythema, erythema multiforme, exacerbation of myasthenia gravis, eye infection, facial paresis, focal facial paralysis, hyperhidrosis, hypersensitivity reaction, hypoacusis, hypoesthesia, inflammation at injection site, jaw pain, lagophthalmos, madarosis of the eyebrow, malaise, muscle twitching (localized), myalgia, myocardial infarction, nerve root disorder, paresthesia, peripheral neuropathy, photophobia, pneumonia, psoriasiform eruption, reduced blinking, respiratory depression, respiratory failure, retinal vein occlusion, retrobulbar hemorrhage, seizure, serum sickness, syncope, tinnitus, urinary incontinence, urticaria, vertigo, visual disturbance, voice disorder, vomiting.

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Safety Precautions: Describe the procedures for protecting against or minimizing any potential risks, *including risks of breach of confidentiality or invasion of privacy*. Where appropriate, discuss provisions for ensuring necessary medical or professional intervention in the event of adverse events, or unanticipated problems involving subjects. Also, where appropriate, describe the provisions for monitoring the data collected to ensure the safety of subjects. If vulnerable populations other than adults with impaired consent capacity are to be recruited, describe additional safeguards for protecting the subjects' rights and welfare.

To guarantee protection to participants of this research study, the medical charts where the information is kept will be stored and handled according to standard procedures. Subjects eligible will voluntarily agree to participate in this study, returning a signed copy of the informed consent form. These consent forms will be kept on a locked cabinet in the PIs office separated from their medical charts or any other identifiable document. An identification number will be assigned to each participant on a database that will be stored in the PIs computer which will be only accessible to the study personnel by means of two passwords. The PI office is kept locked at all times. A database with the coded data will be stored in the PIs computer password protected. All informed consent forms, raw data and the database that link the patient's name to the participant's identification number will be destroyed after 6 years of completion of the study. All team members are compliant with the CITI certification.

Benefit vs. Risk: Describe potential benefits to the subject(s); include potential benefits to society and/or general knowledge to be gained. Describe why the risks to subjects are reasonable in relation to the anticipated benefit(s) to subjects and in relation to the importance of the knowledge that may reasonably be expected to result. If you are using vulnerable subjects (e.g., impaired consent capacity, pregnant women, etc…), justify their inclusion by describing the potential benefits of the research in comparison to the subjects' vulnerability and the risks to them. For information about inclusion of certain vulnerable populations, see the IRB/ORI Standard Operating Procedure for Protection of Vulnerable Subjects [C3.0100] [PDF].

Participants in this study may receive pain relief from the infiltration of onabotulinum toxin A for the management of neuropathic pain, which a chronic disabling condition. Nowadays, there is not a definitive treatment for neuropathic pain conditions in general. Moreover, therapy is often limited to pain management which is insufficiently achieved with the available pharmacotherapy. The medications can be administered as monotherapy or polytherapy and include the following: anticonvulsants, antidepressants, topical medications, anesthetic blocks, etc. Additionally, these medications are not always well tolerated by patients due to the side effects. Therefore, there is a need to research better management options. onabotulinum toxin A has demonstrated to have therapeutic benefit for other neuropathic pain conditions in other areas of the body, as well as, for the management of chronic migraines. Both conditions seem to share similar pathophysiology with the dentoalevolar continuous neuropathic pain. As described in the previous paragraph the potential risks are not frequent and in most cases they are transient.

Available Alternative Treatment(s): Describe alternative treatments and procedures that might be advantageous to the subjects, should they choose not to participate in the study. This should include a discussion of the current standard of care treatment(s).

As mentioned before, neuropathic pain can be managed by pharmacotherapy, which can be provided as monotherapy or polytherapy including: anticonvulsants, antidepressants, topical medications, anesthetic blocks, etc. However, these medications frequently are not tolerated by patients due to side effects including: drowsiness, dizziness, fatigue, cognitive impairment, among others.

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Research Materials, Records and Privacy: Identify the sources of research material obtained from individually identifiable living human subjects. Indicate what information (specimens, records, data, genetic information, etc.) will be recorded and whether use will be made of existing specimens, records or data. Explain why this information is needed to conduct the study.

Return of Research Results or Incidental Findings (if applicable):
If research has the potential to identify individual results or discover incidental findings that could affect the health of a subject, describe plans to assess, manage, and if applicable disclose findings with individual subjects or provide justification for not disclosing. For IRB expectations, refer to the UK IRB "Frequently Asked Questions (FAQs) on the Return of Research Results or Incidental Research Findings" [PDF].

This study use information contained in patient's chart in addition to information obtained from daily pain surveys and two phone interviews. The data collected from the patient's chart include: demographics including: gender, age, occupation, and marital status. Disease diagnosis and information from the clinical examination such as location of pain, presence of sensory deficits, and response to application of local anesthetic. Results from the psychological and pain questionnaires completed by the patient at their initial evaluation (see attachments). These data will be collected from the patient's chart as part of the standard of care. In addition, results from the pain surveys will be collected as part of the research project, as well as the information collected from follow up phone interview. These data will be collected for research purposes.

Confidentiality: Specify where the data/specimens will be stored and how the researcher will protect both the data and/or specimens with respect to privacy and confidentiality. Address physical security measures (e.g., locked facility, limited access); data security (e.g., password-protection, data encryption); safeguards to protect identifiable research information (e.g., coding, links, certificate of confidentiality); and procedures employed when sharing material or data, (e.g., honest broker (if applicable), written agreement with recipient not to re-identify). If you plan to procure, store, and/or share material (tissue/specimens/data) expressly for use in current or future research, describe measures that you will take to secure and safeguard confidentiality and privacy.

Provide a time table for destroying the data/specimens and identify how they will be destroyed, or provide rationale for perpetual maintenance [Note: The investigator is responsible for retaining the signed consent and assent documents and IRB research records for at least six years after study closure as outlined in the Study Closure SOP [PDF]. If the research falls under the authority of FDA or

other regulatory agency, the investigator is responsible for retaining the signed documents and IRB records for the period specified if longer than six years after completion of the study]. For multi-site studies, the PI consults the study sponsor regarding retention requirements, but must maintain records for a minimum of six years after study closure. Also, specify who will access the identified data/specimens, and why they need access. If applicable, describe what measures will be taken to ensure that subject identifiers are not given to the investigator. If applicable, describe procedures for sharing data/specimens with entities not affiliated with UK.

> *NIH-funded genomic research*: The National Institutes of Health (NIH) Genomic Data Sharing (GDS) Policy sets forth expectations that ensure the broad and responsible sharing of genomic research data consistent with the informed consent of study participants from which the data was obtained. If you are submitting genomic data to an NIH data repository, describe your NIH data sharing plan.

Please note: The IRB expects researchers to access the minimal amount of identifiers to conduct the study and comply with applicable HIPAA and Family Educational Rights and Privacy Act (FERPA) requirements. If data are going to be collected, transmitted, and/or stored electronically, for appropriate procedures please refer to the guidance document "Confidentiality and Data Security Guidelines for Electronic Data" [PDF].

Also please note that storage of data on cloud services may not be appropriate and is subject to applicable university policies regarding the use of cloud services. If deemed too sensitive or inappropriate to be stored or collected using cloud services, the IRB may require an alternate method of data storage in accordance with applicable university policies and the electronic data security guidance document referenced above.

If a research protocol involves the creation and/or use of a computer program or application, mobile or otherwise, please specify whether the program/application is being developed by a commercial software developer or the research team and provide any relevant information regarding the security and encryption standards used, how data is stored and/or transmitted to the research team, what information about the subjects the program/application will collect, etc. For relevant information to include, see Considerations for Protocol Design Concerning Digital Data [PDF]. The IRB may require software programs created or used for research purposes be examined by a consultant with appropriate Internet technology expertise to ensure subject privacy and data are appropriately protected.

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All participants will be informed that research records will be kept confidential to full extent allowed by the law. This study uses information contained in patients' chart. The charts are handled and preserved by standard protocols. Informed consent forms signed by patients that agreed to participate in this research study will be stored in a locked cabinet at the PIs office which is kept locked at all times. A password protected database containing the link between the patient's name and the participant's identification number will be stored in the PI's computer located in room E236 Orofacial Pain Center, second floor of the Kentucky Clinic. A log on password is required to access this computer. This office is located inside of the Orofacial Pain Center and has limited access. This office it is kept locked at all times. The coded data will be entered in a separated database password protected, stored in the PI's computer in room and will only be accessible to the PIs and study personnel. Throughout the duration of the study, only members of the research team will have access to study data. Additionally, the pain survey will be completed online through RedCap. REDCap is a secure, web-based program to capture and store data at the University of Kentucky. Research findings that are published will not contain any identifying information about participants.

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Payment: Describe the incentives (e.g., inducements) being offered to subjects for their time during participation in the research study. If monetary compensation is offered, indicate how much the subjects will be paid and describe the terms and schedule of payment. (It is IRB policy that provision should be made for providing partial payment to subjects who withdraw before the completion of the research. Monetary payments should be prorated or paid in full.)

In this study no reward/payment is involved,

Costs to Subjects: Describe any costs for care associated with research (including a breakdown of standard of care procedures versus research procedures), costs of test drugs or devices, and research procedure costs that are the subject's responsibility as a consequence of participating in the research. Describe any offer for reimbursement of costs by the sponsor for research related injury care.

No additional costs will be charged to the patient since this project reviews charts for patients attending routine clinical visits. The onabotulinum toxin A will be provided by Allergan Sales, LLC. Each bottle of 100 units of onabotulinum toxin A cost $600, needled and syringes will be obtained from the Orofacial Pain Clinic. Patients will not receive any reimbursement for their participation in the study. Allergan Sales, LLC. will not provide any compensation for any research-related injuries resulting or related to the study.

Data and Safety Monitoring: The IRB requires review and approval of data and safety monitoring plans for greater than minimal risk research, clinical research, or NIH-funded/FDA-regulated clinical investigations.

If you are conducting greater than minimal risk research, clinical research, or your clinical investigation is NIH-funded/FDA-regulated, describe your Data and Safety Monitoring Plan (DSMP). Click here for additional guidance on developing a Data and Safety Monitoring Plan.

If this is a *non-sponsored investigator-initiated* protocol considered greater than minimal risk research, clinical research, or your clinical investigation is FDA-regulated, *and* if you are planning on using a Data and Safety Monitoring Board (DSMB) as part of your DSMP, click here for additional guidance for information to include with your IRB application.

If relying on an independent agent or committee for DSMB services, it is the PI's responsibility to establish the services with the agent or committee. Please be reminded that the PI must submit DSMB reports to the IRB via modification or continuing review.

1. Data Quality and Safety of Participants Monitoring: Subjects involved in this research will be contacted by the PI through a phone call to monitor any side effects or adverse reactions one week after the intraoral administration of onabotulinum toxin A. In addition, patients will be recommended to contact the PI immediately if any side effects are noted, in case there is a medical emergency patients are recommended to contact 911 immediately. Subjects will also be completing on a daily basis a survey regarding any potential side effects that could be developed. If the patient reports any adverse events, they will be asked to return to the Orofacial Pain Clinic for reevaluation. Any adverse events observed during the development of the study will be discussed with the co-investigator, faculty advisor included in the study and reported to an independent monitor. Any serious adverse event that occur during the course of the study will be disclosed to the United States Food and Drug Administration (FDA) following the FDA requirements for safety reporting as outlined in 21 CFR §§803.10 – 803.22; §§803.30 – 803.33 and 21 CFR §312.32. A written notice will also be provided to Allergan Sales, LLC in the event of any serious adverse events. Forms GPSE-POVPS-F02-01_Interventional SAE form; 02-03_Non-interventional SAE form and 02-06_Pregnancy forms will be completed. A report of unanticipated problems or adverse experiences will be submitted through the E-IRB website. PI and co-investigator will review quarterly for data completeness and accuracy as well as protocol compliance, and double-data entry will be performed for data verification. The data will be reviewed quarterly including: recruitment of participants (compliance with enrollment criteria), status of all participants as of date of reporting, adherence data regarding study visits and intervention. Any adverse events will be reported at the time of the occurrence. Progress reports will be provided to the Independent Monitor quarterly including: recruitment of participants (compliance with enrollment criteria), status of all participants as of date of reporting, adherence data regarding study visits and intervention. Any adverse events will be reported at the time of the occurrence by utilizing the abovementioned forms. An Annual Report will be compiled and will include a list and summary of AEs. In addition, the Annual Report will address (1) whether AE rates are consistent with pre-study assumptions; (2) reason for dropouts from the study; (3) whether all participants met entry criteria; (4) whether continuation of the study is justified on the basis that additional data are needed to accomplish the stated aims of the study; and (5) conditions whereby the study might be terminated prematurely. The Annual Report will be sent to the Independent Monitor and will be forwarded to the IRB. 2. Independent Monitor: The independent monitor for this study is Dr. Kevin Nelson. Dr. Nelson is not associated with this research project and thus works independently of the PI, Dr. Isabel Moreno Hay. Dr. Nelson is not a part of the key personnel involved in this grant, and is qualified to review the patient safety data generated by this study because of his unique expertise in the clinical use of onabotulinum toxin A injections. 3. Reporting changes in the study status: The PI will notify Allergan Sales, LLC. in writing, if for any reason is unable or unwilling to complete or direct the performance of the study; is unable or unwilling to meet enrollment and other requirements as set forth in the study; receives a rejection of the study protocol by the appropriate IRB; receives notice that the FDA has placed the IDE on clinical hold, if applicable; postpones the study for a period in excess of six (6) months; makes a material change to the Study protocol, or intends to abandon the study. The termination of the study may occur by mutual written consent of Allergan Sales, LLC and the PI; by either party upon thirty (30) days prior written notice; immediately upon material breach which remains uncured for thirty (30) days following the breaching party's receipt of written notice from the non-breaching party; or by either party for study subject safety concerns effective immediately upon written notice to the other party. Immediately upon receipt of any notice of termination of the agreement between Allergan Sales, LLC and the PI prior to completion of the Study, the PI will stop entering subjects into the Study; undertake all reasonable efforts to minimize further costs; submit a final study report to Allergan Sales, LLC.; and cease the use of the materials to the extent medically permissible on subjects already enrolled in the Study.

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Subject Complaints: Describe procedures (other than information provided in consent document) for handling subject complaints or requests for information about the research. The procedures should offer a safe, confidential, and reliable channel for current, prospective, or past research subjects (or their designated representative) permitting them to discuss problems, concerns and questions, or obtain information.

Patients concerns and complaints in regard to this study will be made through the Orofacial Pain Center office directly to the PIs (Isabel Moreno Hay, DDS PhD). This information will remain confidential and the PI will provide the best information possible to the patient. The participants will keep a copy of the informed consent form which contains the contact information of the PIs and the University of Kentucky's Office of Research Integrity.

Does your research involve **Non-English Speaking Subjects or Subjects from a Foreign Culture**?

○ Yes ◉ No

Non-English Speaking Subjects or Subjects from a Foreign Culture

Describe how information about the study will be communicated to potential subjects appropriate for their culture, and if necessary, how new information about the research may be relayed to subjects during the study.

Include contact information for someone who can act as a cultural consultant for your study. The person should be familiar with the culture of the subject population and/or be able to verify that translated documents are the equivalent of the English version of documents submitted. The consultant should not have any direct involvement with the study. If you do

not know someone who would be willing to act as your cultural consultant, the Office of Research Integrity will try to find someone to fill this role (this may delay the approval process for your protocol). Please include the name, address, telephone number, and email of the person who will act as the cultural consultant for your study. For more details, see the IRB Application Instructions on Research Involving Non-English Speaking Subjects or Subjects from a Foreign Culture.

For recruitment of Non-English speaking subjects, the consent document needs to be in the subject's native language. Download the informed consent template available in the E-IRB "Informed Consent/Assent Process" section and use it as a guide for developing the consent document. (Note: Your translated consent document can be attached to your application in the "Informed Consent" section; **be sure to save your responses in this section first**.)

If research is to be conducted at an international location, identify local regulations, laws, or ethics review requirements for human subject protection. If the project has been or will be reviewed by a local Ethics Committee, attach a copy of the review to the UK IRB using the attachment button below. You may also consult the current edition of the International Compilation of Human Research Standards

Does your study involve **HIV/AIDS research and/or screening for other reportable diseases (e.g., Hepatitis C, etc…)**?

○ Yes ◉ No

HIV/AIDS Research

If you have questions about what constitutes a reportable disease and/or condition in the state of Kentucky, see ORI's summary sheet: "Reporting Requirements for Diseases and Conditions in Kentucky" [PDF].

HIV/AIDS Research: There are additional IRB requirements for designing and implementing the research and for obtaining informed consent. Describe additional safeguards to minimize risk to subjects in the space provided below.

For additional information, visit the online IRB Survival Handbook to download a copy of the "Medical IRB's requirements for Protection of Human Subjects in Research Involving HIV Testing" [D65.0000] [PDF], and visit the Office for Human Research Protections web site for statements on AIDS research, or contact the Office of Research Integrity at 859-257-9428.

PI-Sponsored FDA-Regulated Research

Is this an investigator-initiated study that:

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1) involves testing a Nonsignificant Risk (NSR) Device, or
2) is being conducted under an investigator-held Investigational New Drug (IND) or Investigational Device Exemption (IDE)?

○ Yes ◉ No

PI-Sponsored FDA-Regulated Research

If the answer above is yes, then the PI assumes the regulatory responsibilities of both the investigator and sponsor. The Office of Research Integrity provides a summary list of sponsor IND regulatory requirements for drug trials [PDF], IDE regulatory requirements for SR device trials [PDF], and abbreviated regulatory requirements for NSR device trials [PDF]. For detailed descriptions see FDA Responsibilities for Device Study Sponsors or FDA Responsibilities for IND Drug Study Sponsor-Investigators.

- Describe your (the PI's) experience/knowledge/training (if any) in serving as a sponsor (e.g., previously held an IND/IDE); and
- Indicate if you have transferred any sponsor obligations to a commercial sponsor, contract research organization (CRO), contract monitor, or other entity (provide details or attach FDA 1571).

IRB policy requires mandatory training for all investigators who are also FDA-regulated sponsors (see Sponsor-Investigator FAQs). A sponsor-investigator must complete the applicable Office of Research Integrity web based training, (drug or device) before final IRB approval is granted.

Has the PI completed the mandatory PI-sponsor training prior to this submission?

○ Yes ○ No

If you (the PI) have completed equivalent sponsor-investigator training, you may submit documentation of the content for the IRB's consideration.

Attachments

HIPAA

Is HIPAA applicable? ◉ Yes ○ No

(Visit ORI's Health Insurance Portability and Accountability Act (HIPAA) web page to determine if your research falls under the HIPAA Privacy Regulation.)

If yes, check below all that apply and attach the applicable document(s):

☐ HIPAA De-identification Certification Form

☑ HIPAA Waiver of Authorization

Attachments

Attach Type	File Name
CombinedInformedConsent	10160-Form_C_Med_and_HIPAA_BOTOX_rev_1_not_highlighted.pdf
HighlightedChanges	10160-Form_C_Med_and_HIPAA_BOTOX_rev_1_highlighted.pdf
Waiver	10700-Form-K_HIPAA_Waiver_Of_Authorization_Form.pdf
Waiver	10700-Form-K_HIPAA_Waiver_Of_Authorization_Form_rev 1.pdf

STUDY DRUG INFORMATION

The term drug may include:

- FDA approved drugs,
- unapproved use of approved drugs,
- investigational drugs or biologics,
- other compounds or products intended to affect structure or function of the body, and/or
- complementary and alternative medicine products such as dietary supplements, substances generally recognized as safe (GRAS) when used to diagnose, cure mitigate, treat or prevent disease, or clinical studies of e-cigarettes examining a potential therapeutic purpose.

Does this protocol involve testing (collecting safety or efficacy data) of a drug including an FDA approved drug, unapproved use of an FDA approved drug and/or an investigational drug?

◉ Yes ○ No

If yes, complete the questions below. Additional study drug guidance.

LIST EACH DRUG INVOLVED IN STUDY IN THE SPACE BELOW

Drug Name:

onabotulinumtoxinA

Note: Inpatient studies are required by Hospital Policy to utilize the Investigational Drug Service (IDS). Use of IDS is highly recommended, but optional for outpatient studies. Outpatient studies not using IDS services are subject to periodic inspection by the IDS for compliance with drug accountability good clinical practices.

Indicate where study drug(s) will be housed and managed:

☐ Investigational Drug Service (IDS) UK Hospital

Other Location:

Orofacial Pain Clinic, Kentucky Clinic, UK Healthcare

Is the study being conducted under a valid Investigational New Drug (IND) application?

○ Yes ◉ No

If Yes, list IND #(s) and complete the following:

IND Submitted/Held by:

Sponsor: ☐ Held By:

Investigator: ☐ Held By:

Other: ☐ Held By:

☐ Checkmark this if the study is being conducted under FDA's Expanded Access Program (e.g., Treatment IND).

- FDA's Expanded Access Program Information (e.g., treatment IND)
- Guidance and definitions: "Expanded Access SOP" (PDF).

Please also complete and attach the Study Drug Form (PDF) (required):

Attachments

Attach Type	File Name
StudyDrug	Study Drug Attachment(for PDF).pdf

STUDY DEVICE INFORMATION

A DEVICE may be a:

- component, part, accessory;
- assay, reagent, or in-vitro diagnostic device;
- software, digital health, or mobile medical app;
- other instrument if intended to affect the structure or function of the body, diagnose, cure, mitigate, treat or prevent disease; or
- a homemade device developed by an investigator or other non-commercial entity and not approved for marketing by FDA.

For additional information, helpful resources, and definitions, see ORI's Use of Any Device Being Tested in Research web page.

Does this protocol involve testing (collecting safety or efficacy data) of a medical device including an FDA approved device, unapproved use of an approved device, humanitarian use device, and/or an investigational device?

○ Yes ◉ No

[Note: If a marketed device(s) is only being used to elicit or measure a physiologic response or clinical outcome, AND, NO data will be collected on or about the device itself, you may answer “no” above, save and exit this section, (Examples: a chemo drug study uses an MRI to measure tumor growth but does NOT assess how effective the MRI is at making the measurement; an exercise study uses a heart monitor to measure athletic performance but no safety or efficacy information will be collected about the device itself, nor will the data collected be used for comparative purposes against any other similar device).]

If you answered yes above, please complete the following questions.

LIST EACH DEVICE BEING TESTED IN STUDY IN THE SPACE BELOW

Device Name:

Is the study being conducted under a valid Investigational Device Exemption (IDE) or Humanitarian Device Exemption (HDE) application? See UK HUD SOP (PDF) for guidance.

○ Yes ○ No

If Yes, list IDE or HDE #(s) and complete the following:

IDE/HDE Submitted/Held by:

Sponsor: ☐ Held By:

Investigator: ☐ Held By:

Other: ☐ Held By:

☐ Check if this is a Treatment or Compassionate Use IDE under the Food and Drug Administration (FDA) Early Expanded Access program.

- FDA's Early Expanded Access Program Information
- Guidance and definitions: "Medical Device Clinical Investigations, Compassionate Use, and Treatment IDE SOP" (PDF)

Does the intended use of any device used in this study meet the regulatory definition of Significant Risk (SR) device?

○ Yes. Device(s) as used in this study presents a potential for serious risk to the health, safety, or welfare of a subject and (1) is intended as an implant; or (2) is used in supporting or sustaining human life; or (3) is of substantial importance in diagnosing, curing, mitigating or treating disease, or otherwise prevents impairment of human health; or (4) otherwise presents a potential

for serious risk to the health, safety, or welfare of a subject.

○ No. All devices, as used in this study do not present a potential for serious risk to the health, safety, or welfare of subjects/participants.

Please also complete and attach the Study Device Form (PDF) (required):

Attachments

RESEARCH SITES

In order for this section to be considered complete, you must click "SAVE" after ensuring all responses are accurate.

A) Check all the applicable sites listed below at which the research will be conducted. If none apply, you do not need to check any boxes.

UK Sites

- ☐ UK Classroom(s)/Lab(s)
- ☑ UK Clinics in Lexington
- ☐ UK Clinics outside of Lexington
- ☐ UK Healthcare Good Samaritan Hospital
- ☐ UK Hospital

Schools/Education Institutions

- ☐ Fayette Co. School Systems *
- ☐ Other State/Regional School Systems
- ☐ Institutions of Higher Education (other than UK)

***Fayette Co. School systems, as well as other non-UK sites, have additional requirements that must be addressed. See ORI's IRB Application Instructions - Off-site Research web page for details.**

Other Medical Facilities

- ☐ Bluegrass Regional Mental Health Retardation Board
- ☐ Cardinal Hill Hospital
- ☐ Eastern State Hospital
- ☐ Norton Healthcare
- ☐ Nursing Homes
- ☐ Shriner's Children's Hospital
- ☐ Veterans Affairs Medical Center
- ☐ Other Hospitals and Med. Centers

- ☐ Correctional Facilities
- ☐ Home Health Agencies
- ☐ International Sites

List all other non-UK owned/operated locations where the research will be conducted:*

*A letter of support and local context is required from non-UK sites. See *Letters of Support and Local Context* on the IRB Application Instructions - Off-Site Research web page for more information.

Attachments

B) Is this a multi-site study for which you are the lead investigator or UK is the lead site? ○ Yes ◉ No

If **YES**, you must describe the plan for the management of reporting unanticipated problems, noncompliance, and submission of

protocol modifications and interim results from the non-UK sites in the E-IRB "Research Description" section under *Resources*.

If the non-UK sites or non-UK personnel are *engaged* in the research, there are additional federal and university requirements which need to be completed for their participation, such as the establishment of a cooperative IRB review agreement with the non-UK site. Questions about the participation of non-UK sites/personnel should be discussed with the ORI staff at (859) 257-9428.

RESEARCH ATTRIBUTES

Indicate the items below that apply to your research. Depending on the items applicable to your research, you may be required to complete additional forms or meet additional requirements. Contact the ORI (859-257-9428) if you have questions about additional requirements.

☐ Not applicable

Check All That Apply

	Click applicable listing(s) for additional requirements and/or information:
☐ Academic Degree/Required Research	
☐ Aging Research	
☐ Alcohol Abuse Research	
☐ Cancer Research	• Cancer Research (MCC PRMC)
☐ Certificate of Confidentiality	• Certificate of Confidentiality (look up "Confidentiality/Privacy...")
☐ CCTS-Center for Clinical & Translational Science	• CCTS (Center for Clinical and Translational Science)
☑ Clinical Research	• Clinical Research (look up "What is the definition of....)
☑ Clinical Trial	• Clinical Trial (look up "What is the definition of....) Determine if research meets NIH definition of clinical trial; *Reminder: Ensure compliance with clinicaltrials.gov registration requirements for applicable clinical trials and Good Clinical Practice (GCP) training requirements.
☐ Clinical Trial Multicenter(excluding NIH Cooperative Groups)	
☐ Clinical Trial NIH cooperative groups (i.e., SWOG, RTOG)	
☐ Clinical Trial Placebo Controlled Trial	
☑ Clinical Trial UK Only	
☐ Collection of Biological Specimens	• Collection of Biological Specimens for Banking (look up "Specimen/Tissue Collection...")
☐ Collection of Biological Specimens for Banking	• Collection of Biological Specimens (look up "Specimen/Tissue Collection...")
☐ Community-Based Participatory Research	• Community-Based Participatory Research (look up "Community-Engaged...")
☐ Data & Safety Monitoring Board	• Data & Safety Monitoring Board
☐ Data & Safety Monitoring Plan	• Data & Safety Monitoring Plan
☐ Deception	• Deception* *For deception research, also go to the E-IRB Application Informed Consent section, checkmark and complete "Request for Waiver of Informed Consent Process"
☐ Drug/Substance Abuse Research	
☐ Educational/Student Records (e.g., GPA, test scores)	
☐ Emergency Use (Single Patient)	• Emergency Use (Single Patient) [attach Emergency Use Checklist] (PDF)
☐ Genetic Research	• Genetic Research (look up "Specimen/Tissue Collection...")
☐ Gene Transfer	• Gene Transfer
☐ GWAS (Genome-Wide Association Study) or NIH-funded study generating large scale genomic data	• HIV/AIDS Research (look up "Reportable Diseases/Conditions")
☐ International Research	• Screening for Reportable Diseases [E2.0000] (PDF)
☐ Internet Research	• International Research (look up "International & Non-English Speaking")
☐ Planned Emergency Research Involving Waiver of Informed Consent	• Planned Emergency Research Involving Waiver of Informed Consent* *For Planned Emergency Research Involving Waiver of Informed Consent, also go to the E-IRB Application Informed Consent section, checkmark and complete "Request for Waiver of Informed Consent Process"
☐ Pluripotent Stem Cell Research	
☐ Recombinant DNA	
☐ Survey Research	
☐ Transplants	
☐ Use of radioactive material, ionizing radiation, or x-rays [Radiation Safety Committee review required]	• Use of radioactive material, ionizing radiation or x-rays for research
☐ Vaccine Trials	

FUNDING/SUPPORT

If the research is being submitted to, supported by, or conducted in cooperation with an external or internal agency or funding program, indicate below all the categories that apply.

☐ Not applicable

Check All That Apply

- ☐ Grant application pending
- ☐ (HHS) Dept. of Health & Human Services
  - ☐ (NIH) National Institutes of Health
  - ☐ (CDC) Centers for Disease Control & Prevention
  - ☐ (HRSA) Health Resources and Services Administration
  - ☐ (SAMHSA) Substance Abuse and Mental Health Services Administration
- ☐ (DoJ) Department of Justice or Bureau of Prisons
- ☐ (DoE) Department of Energy
- ☐ (EPA) Environmental Protection Agency
- ☐ Federal Agencies Other Than Those Listed Here
- ☐ Industry (Other than Pharmaceutical Companies)
- ☐ Internal Grant Program w/ proposal
- ☐ Internal Grant Program w/o proposal
- ☐ National Science Foundation
- ☐ Other Institutions of Higher Education
- ☑ Pharmaceutical Company
- ☐ Private Foundation/Association
- ☐ U.S. Department of Education
- ☐ State

Other:

Click applicable listing(s) for additional requirements and/or information:

- (HHS) Dept. of Health & Human Services
- (NIH) National Institutes of Health
- (CDC) Centers for Disease Control & Prevention
- (HRSA) Health Resources & Services Administration
- (SAMHSA) Substance Abuse & Mental Health Services Administration
- Industry (Other than Pharmaceutical Companies) [IRB Fee Info]
- National Science Foundation
- (DoEd) U.S. Department of Education
- (DoJ) Department of Justice or Bureau of Prisons
- (DoE) Department of Energy Summary and Department of Energy Identifiable Information Compliance Checklist
- (EPA) Environmental Protection Agency

Specify the funding source and/or cooperating organization(s) (e.g., National Cancer Institute, Ford Foundation, Eli Lilly & Company, South Western Oncology Group, Bureau of Prisons, etc.):

Allergan Sales, LLC

Add Related Grants

If applicable, please search for and select the OSPA Account number or Electronic Internal Approval Form (eIAF) # (notif #) associated with this IRB application:

Add Related Grants

Grant/Contract Attachments

The research involves use of Department of Defense (DoD) funding, military personnel, DoD facilities, or other DoD resources. (See DoD SOP [PDF] and DoD Summary [PDF] for details)

○ Yes ◉ No

Using the “attachments” button (below), attach applicable materials addressing the specific processes described in the DoD SOP.

DOD SOP Attachments

Additional Certification: (If your project is federally funded, your funding agency may request an Assurance/ Certification/Declaration of Exemption form.) Check the following if needed:

☐ Protection of Human Subjects Assurance/Certification/Declaration of Exemption (Formerly Optional Form – 310)

OTHER REVIEW COMMITTEES

If you check any of the below committees, additional materials may be required with your application submission.

Does your research fall under the purview of any of the other review committees listed below? [*If yes, check all that apply and attach applicable materials using the attachment button at the bottom of your screen.*]

○ Yes ◉ No

☐ Institutional Biosafety Committee
☐ Radiation Safety Committee
☐ Radioactive Drug Research Committee
☐ Markey Cancer Center (MCC) Protocol Review and Monitoring Committee (PRMC)
☐ Graduate Medical Education Committee (GME)
☐ Office of Medical Education (OME)

Additional Information

- Institutional Biosafety Committee (IBC)--Attach required IBC materials
- Radiation Safety Committee (RSC)-- For applicability, see instructions and/or upload form [WORD] [PDF]
- Radioactive Drug Research Committee (RDRC)--information
- Markey Cancer Center (MCC) Protocol Review and Monitoring Committee (PRMC)**--Attach MCC PRMC materials, if any, per instructions
- See requirement of Office of Medical Education (OME)
- See requirement of Graduate Medical Education Committee (GME)

Attachments

**** If you are proposing a study involving cancer research, be sure to have "Cancer Research" marked in the E-IRB "Research Attributes" section.** If your study involves cancer research, ORI will provide a copy of your research protocol to the Markey Cancer Center (MCC) Protocol Review and Monitoring Committee (PRMC). The MCC PRMC is responsible for determining whether the study meets the National Cancer Institute (NCI) definition of a clinical trial and for issuing documentation to you (the investigator) which confirms either that PRMC approval has been obtained or that PRC review is not required. Your IRB application will be processed and reviewed independently from the PRMC review.

ADDITIONAL INFORMATION/MATERIALS

Do you want specific information inserted into your approval letter? ○ Yes ◉ No

Approval Letter Details (e.g., serial #):

Submission Description: If you wish to have specific details included in your approval letter (e.g., serial #, internal tracking identifier, etc…), type in the box below exactly what you wish to see on the approval letter. What you type will automatically appear at the top of all approval letters, identical to how you typed it, until it is changed by you (Hint: don't include instructions or questions to ORI staff as those will appear in your approval letter). **If these details need to be changed as a result of revisions, continuation review, or modifications to the application, you are responsible for updating the content of the field below accordingly.**

Protocol/Product Attachments - For each item checked, please attach the corresponding material.

- ☐ Detailed protocol
- ☐ Dept. of Health & Human Services (DHHS) approved protocol (such as NIH sponsored Cooperative Group Clinical Trial)
- ☑ Drug Documentation (e.g., Investigator Brochure; approved labeling; publication; FDA correspondence, etc.)
- ☐ Device Documentation (e.g., Manufacturer information; patient information packet; approved labeling; FDA correspondence, etc.)
- ☐ Other Documents

Protocol/Product Attachments

Attach Type	File Name
AddInfoProduct	Lexicomp Online_Botox_monograph.pdf
AddInfoProduct	Botox_FDA_approved_labeling.pdf

NOTE: [Instructions for Dept. of Health & Human Services (DHHS)-approved protocol]

If you have password protected documents, that feature should be disabled prior to uploading to ensure access for IRB review.

Additional Materials:

If you have other materials you would like to include in your application for the IRB's consideration, please attach using the Attachments button below.

[To view what materials are currently attached to your application, go to "Application Links" in the menu bar on the left and click "All Attachments".]

Attachments

Attach Type	File Name
AdditionInfoConsiderations	Email trail between ORI staff and PI about detailed protocol.pdf
AdditionInfoConsiderations	45231 Moreno Hay Revisions Letter.pdf

SIGNATURES (ASSURANCES)

On all IRB applications there is a requirement for additional assurances by a Department Chairperson (or equivalent) [hereafter referred to as "Department Authorization"], and when applicable, a Faculty Advisor (or equivalent), which signifies the acceptance of certain responsibilities and that the science is meritorious and deserving of conduct in humans.

For a list of responsibilities reflected by signing the Assurance Statement, download the guidance document "What does the Department Chairperson's Assurance Statement on the IRB application mean?"

Required Signatures:

First Name	Last Name	Role	Department	Date Signed	
Ted	Raybould	Department Authorization	Dentistry Oral Health Science	11/02/2018 05:56 PM	View/Sign
Isabel	Moreno Hay	Principal Investigator	Dentistry Oral Health Science	11/01/2018 03:57 PM	View/Sign

Department Authorization

☑ This is to certify that I have reviewed this research protocol and that I attest to the scientific validity and importance of this study; to the qualifications of the investigator(s) to conduct the project and their time available for the project; that facilities, equipment, and personnel are adequate to conduct the research; and that continued guidance will be provided as appropriate. When the principal investigator assumes a sponsor function, the investigator is knowledgeable of the additional regulatory requirements of the sponsor and can comply with them.

*If the Principal Investigator is also the Chairperson of the department, the Vice Chairperson or equivalent should complete the "Department Authorization".

Principal Investigator's Assurance Statement

I understand the University of Kentucky's policies concerning research involving human subjects and I agree:

1. To comply with all IRB policies, decisions, conditions, and requirements;
2. To accept responsibility for the scientific and ethical conduct of this research study;
3. To obtain prior approval from the Institutional Review Board before amending or altering the research protocol or implementing changes in the approved consent/assent form;
4. To report to the IRB in accord with IRB/IBC policy, any adverse event(s) and/or unanticipated problem(s) involving risks to subjects;
5. To complete, on request by the IRB for Full and Expedited studies, the Continuation/Final Review Forms;
6. To notify the Office of Sponsored Projects Administration (OSPA) and/or the IRB (when applicable) of the development of any financial interest not already disclosed;
7. Each individual listed as study personnel in this application has received the mandatory human research protections education (e.g., CITI);
8. Each individual listed as study personnel in this application possesses the necessary experience for conducting research activities in the role described for this research study.
9. To recognize and accept additional regulatory responsibilities if serving as both a sponsor and investigator for FDA regulated research.

☑ Furthermore, by checking this box, I also attest that:

- I have appropriate facilities and resources for conducting the study;
- I am aware of and take full responsibility for the accuracy of all materials submitted to the IRB for review;
- If applying for an exemption, I also certify that the only involvement of human subjects in this research study will be in the categories specified in the Protocol Type: Exemption Categories section.

*You will be able to "sign" your assurance after you have sent your application for signatures (use Submission section). Please notify the personnel required for signing your IRB application after sending for signatures. Once all signatures have been recorded, you will need to return to this section to submit your application to ORI.

SUBMISSION INFORMATION

Each Section/Subsection in the menu on the left must have a checkmark beside it (except this Submission section) indicating the Section/Subsection has been completed; otherwise your submission for IRB review and approval will not be able to be sent to the Office of Research Integrity/IRB.

Please remember to update, when applicable, the Approval Letter Details text box under the Additional Information section to ensure verbiage you want on your approval letter is accurate.

If your materials require review at a convened IRB meeting which you will be asked to attend, it will be scheduled on the next available agenda and a message will be forthcoming to notify you of the date.

If you are making a change to an attachment, you need to delete the attachment, upload a highlighted version that contains the changes (use Document Type of "Highlighted Changes"), and a version that contains the changes without any highlights (use the appropriate Document Type for the item(s)). Do **not** delete approved attachments that are still in use.

Your protocol has been submitted.

	Document Type	File Loaded	Document Description	File Size	Modified By	Mod Date
	Stamped Consent Form	10160-Form_C_Med_and_HIPAA_BOTOX_rev_1_not_highlighted.pdf		0.110	jaro222	2/5/2019 9:04:50 AM
	ApprovalLetter	ApprovalLetter.pdf		0.059	jaro222	2/5/2019 9:04:50 AM
	HighlightedChanges	10160-Form_C_Med_and_HIPAA_BOTOX_rev_1_highlighted.pdf	Consent form with highlighted changes	0.067	imo226	1/25/2019 9:13:45 AM
	CR_DataSafetyMonitoring	Quarterly Report Independent Monitor.docx	Quarterly Report for Independent Monitor	0.013	imo226	1/22/2019 2:24:41 PM
	CR_DataSafetyMonitoring	GPSE-PVOPS-F-02-06.doc (Pregnancy form).doc	Pregnancy Report	0.204	imo226	1/22/2019 2:24:08 PM
	CR_DataSafetyMonitoring	GPSE-PVOPS-F-02-03_Non-interventional SAE form.pdf	Adverse Event Report_Non interventional	0.135	imo226	1/22/2019 2:23:51 PM
	CR_DataSafetyMonitoring	GPSE-PVOPS-F-02-01_Interventional SAE form (002).pdf	Adverse Event Report	0.171	imo226	1/22/2019 2:23:25 PM
	CombinedInformedConsent	10160-Form_C_Med_and_HIPAA_BOTOX_rev_1_not_highlighted.pdf	Revised consent form not highlighted	0.066	imo226	1/16/2019 9:49:04 AM
	Waiver	10700-Form-K_HIPAA_Waiver_Of_Authorization_Form_rev 1.pdf	HIPAA Waiver of authorization with requested modifications	0.084	imo226	1/16/2019 9:47:48 AM
	AdditionInfoConsiderations	45231 Moreno Hay Revisions Letter.pdf	Minor Revisions requested at 1/7/19 IRB Meeting	0.067	jaro222	1/9/2019 7:56:17 AM
	AdditionInfoConsiderations	Email trail between ORI staff and PI about detailed protocol.pdf	E-mail trail between ORI and PI regarding detailed protocol/sponsor	0.170	jaro222	1/2/2019 3:47:27 PM
	AddInfoProduct	Botox_FDA_approved_labeling.pdf	FDA_labeling	0.573	imo226	9/5/2018 5:00:11 PM
	AddInfoProduct	Lexicomp Online_Botox_monograph.pdf	Botox_Monongraph	0.195	imo226	9/5/2018 4:59:59 PM
	StudyDrug	Study Drug Attachment(for PDF).pdf	Form O	0.304	imo226	9/5/2018 4:55:30 PM
	Waiver	10700-Form-K_HIPAA_Waiver_Of_Authorization_Form.pdf		0.083	imo226	9/5/2018 3:25:45 PM
	DataCollection	Psych_package_August_2018.pdf	Psychological questionnaires completed by the patient at their initial evaluation at the Orofacial Pain Clinic (Standard of care)	1.422	imo226	9/5/2018 11:53:59 AM
	DataCollection	Pain New Patient Questionnaire Jul 2018.pdf	Pain questionnaire completed by the patient at their initial evaluation at the Orofacial Pain Clinic (Standard of care)	0.162	imo226	9/5/2018 11:53:04 AM
	DataCollection	Pain Follow Up Questionnaire_phone.pdf	Phone interview one week after the infiltration #1 and #2	0.012	imo226	9/5/2018 11:52:03 AM
			Pain diary to be			9/5/2018

DataCollection	Daily_pain_diary.pdf	completed on a daily basis	0.081	imo226	11:51:01 AM
ImpairedConsent	Form_T_2Ai (1).doc		0.086	imo226	5/30/2018 2:15:08 PM

Protocol Changes

Protocol Number: 45231

StampedConsent changed by imo226 on 1/22/2019 2:25:04 PM

N

WaiverDocICOption3 changed by imo226 on 1/22/2019 2:25:04 PM

N

Research Description DataAndSafetyMonitoring changed by imo226 on 1/22/2019 2:25:44 PM

1. Data Quality and Safety of Participants Monitoring: ¶
Subjects involved in this research will be contacted by the PI through a phone call to monitor any side effects or adverse reactions one week after the intraoral administration of onabotulinum toxin A. In addition, patients will be recommended to contact the PI immediately if any side effects are noted, in case there is a medical emergency patients are recommended to contact 911 immediately. ¶
Subjects will also be completing on a daily basis a survey regarding any potential side effects that could be developed. If the patient reports any adverse events, they will be asked to return to the Orofacial Pain Clinic for reevaluation. ¶
Any adverse events observed during the development of the study will be discussed with the co-inverstigator ~~and,~~ faculty advisor included in the study and reported to an independent monitor. ¶
Any serious adverse event that occur during the course of the study will be disclosed to the United States Food and Drug Administration (FDA) following the FDA requirements for safety reporting as outlined in 21 CFR §§803.10 – 803.22; §§803.30 – 803.33 and 21 CFR §312.32. A written notice will also be provided to Allergan Sales, LLC in the event of any serious adverse events. ¶
~~A report of unanticipated problems or adverse experiences will be submitted through the E-IRB website.~~Forms GPSE-POVPS-F02-01_Interventional SAE form; 02-03_Non-interventional SAE form and 02-06_Pregnancy forms will be completed. ¶
A report of unanticipated problems or adverse experiences will be submitted through the E-IRB website. ¶
PI and co-investigator will review quarterly for data completeness and accuracy as well as protocol compliance, and double-data entry will be performed for data verification. The data will be reviewed quarterly including: recruitment of participants (compliance with enrollment criteria), status of all participants as of date of reporting, adherence data regarding study visits and intervention. Any adverse events will be reported at the time of the occurrence. Progress reports will be provided to the Independent Monitor quarterly including: recruitment of participants (compliance with enrollment criteria), status of all participants as of date of reporting, adherence data regarding study visits and intervention. Any adverse events will be reported at the time of the occurrence by utilizing the abovementioned forms. An Annual Report will be compiled and will include a list and summary of AEs. In addition, the Annual Report will address (1) whether AE rates are consistent with pre-study assumptions; (2) reason for dropouts from the study; (3) whether all participants met entry criteria; (4) whether continuation of the study is justified on the basis that additional data are needed to accomplish the stated aims of the study; and (5) conditions whereby the study might be terminated prematurely. The Annual Report will be sent to the Independent Monitor and will be forwarded to the IRB. ¶
2. Independent Monitor: ¶
The independent monitor for this study is Dr. Kevin Nelson. Dr. Nelson is not associated with this research project and thus works independently of the PI, Dr. Isabel Moreno Hay. Dr. Nelson is not a part of the key personnel involved in this grant, and is qualified to review the patient safety data generated by this study because of his unique expertise in the clinical use of onabotulinum toxin A injections. ¶
3. Reporting changes in the study status: ¶
The PI will notify Allergan Sales, LLC. in writing, if for any reason is unable or unwilling to complete or direct the performance of the study; is unable or unwilling to meet enrollment and other requirements as set forth in the study; receives a rejection of the study protocol by the appropriate IRB; receives notice that the FDA has placed the IDE on clinical hold, if applicable; postpones the study for a period in excess of six (6) months; makes a material change to the Study protocol, or intends to abandon the study. ¶
The termination of the study may occur by mutual written consent of Allergan Sales, LLC and the PI; by either party upon thirty (30) days prior written notice; immediately upon material breach which remains uncured for thirty (30) days following the breaching party's receipt of written notice from the non-breaching party; or by either party for study subject safety concerns effective immediately upon written notice to the other party. Immediately upon receipt of any notice of termination of the agreement between Allergan Sales, LLC and the PI prior to completion of the Study, the PI will stop entering subjects into the Study; undertake all reasonable efforts to minimize further costs; submit a final study report to Allergan Sales, LLC.; and cease the use of the materials to the extent medically permissible on subjects already enrolled in the Study.

Study Personnel Changes:

No Changes

There are no recorded changes to study personnel.

Research Description Comment by Isabel Moreno Hay - PI to PI on 1/22/2019 2:32:34 PM

Changes have been made to the Data Safety Monitor Plan

Research Description Comment by Jessica Williams - ORI to PI on 1/23/2019 8:28:18 AM

For your highlighted consent, please remove the current document and re-attach to "all attachments" as "Highlighted Changes." Highlighted consent should always be under the "highlighted changes" document type so that it does not get stamped with your clean informed consent.

Statistical Analysis Plan

Descriptive statistics were used to summarize demographic and clinical characteristics of the sample. Continuous variables, including age and pain-related outcomes, were reported as means and standard deviations. Categorical variables were summarized using frequencies and percentages.

Pain-related outcomes were derived from patient pain diaries and included average pain. Baseline values were calculated using the 30-day baseline diary period prior to the first intervention. Follow-up values were calculated using 30-day diary averages for each month after the first intervention.

Paired-samples t-tests were used to compare baseline values with follow-up values after the first intervention for average pain. Statistical significance was assessed using two-sided p-values, with an alpha level of 0.05. All analyses were performed using IBM SPSS Statistics.