UF | Institutional Review Board
UNIVERSITY of FLORIDA

INFORMED CONSENT FORM
to Participate in Research, and

AUTHORIZATION
to Collect, Use, and Disclose Protected Health Information (PHI)

INTRODUCTION

Name of person seeking your consent:_____

Place of employment & position: _____

GENERAL INFORMATION ABOUT THIS STUDY

1. Name of Participant ("Study Subject")

_____

2. What is the Title of this research study (this "Research Study")?

Dystonia Treatment With Injections Supplemented by TMS: the D-TWIST study

3. Whom do you call if you have questions about this Research Study (the "Study Team")?

Principal Investigator: John Yu, MD – 352-294-5400

Other research staff: Aparna Wagle Shukla, MD – 352-273-5550

4. Who is paying for this Research Study?

The sponsor of this study is the Dystonia Medical Research Foundation (DMRF).

5. In general, what do you need to know about this Research Study?

Agreeing to become involved in any research is always voluntary. By signing this form, you are not waiving any of your legal rights. If you decide not to participate in this research, you will not be penalized in any way and you will not lose any benefits to which you are entitled. If you have questions about your rights as a research subject, please call the University of Florida Institutional Review Board (IRB) office at (352) 273-9600.

a) In general, what is the purpose of the research, how long will you be involved?

The goal of this study is to find ways to improve treatments for cervical dystonia. We want to know if there are ways to improve the effectiveness of botulinum toxin injections (botox). One type of treatment is called repetitive transcranial magnetic stimulation (rTMS), which is a painless and non-invasive (not breaking, cutting, or entering the skin) treatment that delivers pulses to the brain. To receive rTMS, you will sit reclined in a chair similar to a dentist's chair, a device will be placed close to your head and you will feel a tapping sensation and hear a clicking noise. This is the TMS machine delivering pulses to your brain. We are interested to see if rTMS helps extend or improve the benefit of the botox shots that you are already receiving for your cervical dystonia. For this study, you will continue to receive your regularly scheduled botox shots. We want to know if real rTMS is better than sham (placebo) rTMS, so you will undergo both real and sham rTMS at two different times, but you will not know which type of rTMS you are receiving when you receive it. The rTMS sessions are scheduled around your botox appointments which are every 12 weeks. Therefore, in order to receive both the active and sham rTMS conditions, you will be involved in this study for approximately 24 total weeks.

b) What is involved with your participation, and what are the procedures to be followed in the research?

The schedule of this study is coordinated with your regularly scheduled botox appointments. Nine weeks after your regularly scheduled botox appointment, we will take some measurements to see how your brain functions at baseline. These measurements will include:

-A clinical assessment of the severity of your cervical dystonia
-An electroencephalogram (EEG), in which electrodes (a small device that detects electricity in your body) are placed on your head to measure the electrical activity in your brain. The EEG should take about an hour
-Baseline TMS measurements, where multiple single pulses will make your hand twitch and give us information about your brain activity.
-Your baseline gait parameters by measuring on a gait walkway system in the clinic
-A survey about your mood and some tasks designed to test your cognition (thinking)
-some portions of this study including the EEG, neurologic exam of the dystonia, and gait will be videotaped

After these baseline measurements have been obtained, you will undergo four days of either active or sham rTMS. You will be randomly assigned (like the flipping of a coin) either active or sham rTMS, and will not be aware which type of rTMS you are receiving. Each day of rTMS will last approximately 3 hours. You will feel a tapping sensation on your head and hear a clicking noise. Immediately after each day of rTMS, you will be able to resume your normal activities. These same measurements will be completed after you finish the 4 days of rTMS. Two weeks after you have completed your 4 days of rTMS, you will return for your regularly scheduled botox appointment. At this appointment you will have these measurements repeated a third time. Nine weeks later you will return to repeat the process as described above but this time you will receive either active or sham rTMS, whichever condition you did not

receive before. You will not be aware of which condition (active or sham rTMS) you are receiving when you are receiving it.

c) What are the likely risks or discomforts to you?

TMS: transient discomfort at the stimulation site includes headaches, muscle twitches, toothache, or muscle discomfort. These side effects should not last beyond the rTMS session. There is a possibility of temporary hearing loss due to the noise of the TMS machine, so ear plugs are provided to minimize this risk. There is a rare risk of seizures (abnormal electrical activity in the brain leading to shaking in the body) with rTMS. In the even that you have a seizure, the study staff will immediately stop the treatment session and make sure you are safe. You will be watched for a period of time after the seizure to make sure you are feeling well, and will be removed from further study procedures. Individuals with a known seizure disorder are excluded from participating in this study.

EEG: a gel paste is used to attach the sensors to the scalp which may mildly and briefly irritate the skin.

Surveys: you will be filling out a questionnaire about mood, including questions about depression which may be uncomfortable for some individuals. If the survey reveals significant depression, or thoughts of suicide, you will be referred to appropriate psychiatric and counseling care as needed.

d) What are the likely benefits to you or to others from the research?

You may or may not benefit from taking part in this study. You will continue to receive your regularly scheduled botox injections throughout the duration of this study. All participants will receive both real and sham rTMS in random order. Real rTMS may improve the benefits of botox. rTMS may additionally improve walking, cognition, and mood.

e) What are the appropriate alternative procedures or courses of treatment, if any, that might be helpful to you?

If you choose not to participate in this study, you can discuss other treatment options with your regular doctor, which may include adjusting the botox dose or other medications.

A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This web site will not include information that can identify you. At most, the web site will include a summary of the results. You can search this web site at any time.

Additional and more detailed information is provided within the remainder of this Informed Consent form, please read before deciding if you wish to participate in this study

WHAT CAN YOU EXPECT IF YOU PARTICIPATE IN THIS STUDY?

6. What will be done as part of your normal clinical care (even if you did not participate in this Research Study)?

Your clinical care will not be affected by this study. Any medication regimens you are currently on will not change and you will be expected to continue the same medication regimen you are on at the beginning of the study throughout the duration of the study. You will continue to receive your regularly scheduled botox injections. You will continue to see your regular neurology doctor as scheduled apart from this study.

7. What will be done only because you are in this Research Study?

In order to be eligible for this study, you will need to be receiving botox for cervical dystonia, but only having benefit from the injections for 9 weeks or less. You will also need to be 18 years of age or older, have no history of seizures, have no neurostimulators implanted in your brain (see full list below for implanted devices that are contraindicated), and not be pregnant. Throughout the duration of this study you will be allowed to continue any current medications for your cervical dystonia, and you will be encouraged to remain on the same medication regimen throughout the duration of the study If you fulfill this eligibility criteria, the procedures described below will take place. If you are not eligible to continue, you will return to your regular dystonia care with your regular doctor.

All of the study procedures are scheduled around your regularly scheduled botox appointments, which take place every 12 weeks.

Week 1: You will receive you regularly scheduled botox injections. No additional research study procedures will take place at this time.

Week 9: You will have a series of baseline measurements completed to see how your brain functions at baseline. These measurements include:

-Toronto Western Spasmodic Torticollis Scale (TWSTRS): this is a clinical assessment tool designed to measure the severity of your cervical dystonia
-Electroencephalogram (EEG): electrodes (stickers that measure electrical activity) are placed on the head and will measure the electrical activity in your brain at rest and moving your through a full range of motion. This will take approximately 1 hour.

-TMS measures: multiple single pulses of TMS will be delivered to the brain and make your hand twitch, which will help us to understand how your brain activity acts. This will take approximately 1 hour.

-Cognitive Tasks: you will complete a task connecting numbers and letters called a “Trail-Making Task” and also you will sort cards based on color, number, and shape called the “Wisconsin Card Sorting Task (WCST).” These tasks should take approximately half an hour.
-Beck Depression Inventory (BDI): you will fill out a survey that asks questions about your mood. There are 21 questions asking you to evaluate depression on a 0 to 3 scale and should only take a couple of minutes to complete.

-Gait parameters: you will walk across the Zeno gait walkways system in clinic, which is a walkway that measures specific parameters of your walking. This task you should take a couple of minutes.

Once you have completed the baseline measurements, you will be randomly assigned (like the flipping of a coin) to receive either real of sham rTMS. The rTMS procedures are the same, but in the sham condition there are no real pulses being delivered to the brain. During the rTMS procedures which will occur over the next four days,, you will sit in a reclined chair similar to a dentist chair while receiving rTMS. You will hear a clicking sound and feel a tapping sensation on your head during the rTMS procedure. You are allowed to take a nap or get up for breaks in between sessions. The full rTMS procedure should last about 3 hours each day for 4 days.

Week 10: Following the rTMS procedure, you will undergo the same measurements as listed above.

Week 12: You will return to clinic for your regularly scheduled botox injections. Prior to receiving your botox injections, you will undergo the same measurements as listed above. Afterwards, you will receive your normal botox injections.

Week 21: Nine weeks following your botox injections, you will return and complete the same measurements as listed above. Then you will undergo the same rTMS procedure except you will receive either active or sham rTMS, whichever condition you did not receive the first time.

Week 22: Following the completion of the rTMS protocol, you will have the measurements performed again.

Week 24: You will return to clinic for your regularly scheduled botox injections. Prior to receiving your botox injections, you will undergo the same measurements as listed above. This will be the end of the study. Afterwards, you will receive your normal botox injections.

Once this research study is completed, any information that could identify you **might** be removed from any identifiable private information or identifiable biospecimens collected and that, after such removal, the information or biospecimens could be used for future research studies or distributed to another investigator for future research studies without additional informed consent from you or your legally authorized representative

If you have any questions now or at any time during this Research Study, please contact one of the Research Team members listed in question 3 of this form.

8. What identifiable health information will be collected about you and how will it be used?

The Research Team will collect your name, date of birth, telephone number, email address, geographic location, biometric identifiers, medical record number, dates of data collection, information about your symptoms, including symptom severity and

mental health, and results of research assessments. Your social security number will be collected for monetary compensation purposes.

The Research Team may collect this information from other healthcare providers, such as laboratories, which are a part of this research, as well as healthcare providers that are not part of this research (other doctors, hospitals or clinics). Other professionals at the University of Florida or Shands Hospital who provide study-related care, and the University of Florida Institutional Review Board (IRB), may also collect your health information.

The Research Team listed in question 3 above will use or share your health information as described below to carry out this research study.

9. With whom will this health information be shared?

This health information may be shared with:

- the study sponsor (listed in Question 4 of this form);
- United States governmental agencies which are responsible for overseeing research, such as the Food and Drug Administration, the Department of Health and Human Services, and the Office of Human Research Protections;
- Government agencies which are responsible for overseeing public health concerns such as the Centers for Disease Control and federal, state and local health departments.
- The IRB that reviewed this Research Study and ensures your rights as a Study Subject are protected

Otherwise, your identifiable health information will not be shared without your permission unless required by law or a court order. Once your health information is shared with those listed above, it is possible that they could share it without your permission because it would no longer be protected by the federal privacy law.

10. How long will you be in this Research Study?

You will be participating in this research study for approximately 24 weeks (two rounds of botox injections).

This Authorization to use and share your health information expires at the end of the study, unless you revoke it (take it back) sooner.

11. How many people are expected to take part in this Research Study?

We expect to enroll up to 20 patients in this study and we expect that 10 participants will complete all study procedures.

WHAT ARE THE RISKS AND BENEFITS OF THIS STUDY AND WHAT ARE YOUR OPTIONS?

12. What are the possible discomforts and risks from taking part in this Research Study?

There are some possible discomforts and risks for participants taking part in this study, most of which are mild or transiently related to the study protocol and will abate afterwards.

TMS:

Headaches – Headaches and neck aches can occur. They can be related to stabilizing the neck when measuring TMS. They are usually short lasting and respond easily to over the counter analgesics.

Transient hearing threshold shift – There is a possibility of temporary mild hearing loss due to the noise of the TMS machine; the risk of permanent hearing loss is low... Earplugs will be provided to the participant to reduce the potential for this risk.

Seizure – A seizure is abnormal electrical activity that may cause shaking of the body or lead to loss of consciousness/awareness. A seizure is a theoretical risk associated with brain stimulation. Since FDA clearance of TMS, the seizure risk is ≤0.1% per patient (less than 1 in 1000 patients). In the event that the participant has a seizure, the study staff will immediately stop the treatment session and make sure that the participant is safe during the seizure. The participant will be watched for a period of time after the seizure to make sure he or she is feeling well. Individuals with an active seizure disorder are excluded. If a seizure does occur, you will be removed from continuing with the study.

Fainting – Not directly related to magnetic stimulation. It is thought to be related to anxiety and psycho-physical discomfort during the procedure. The laboratory is equipped, and staff is trained to respond to this risk if fainting occurs. However, the participant will be at very low risk (less than 1%) for fainting. Transfer to the emergency room might be needed if the participant fails to improve as expected.

Effect of Magnetic Stimulation – The NeuroStar TMS Therapy System and MagStim BiStim TMS system is contraindicated for use in patients who have conductive, ferromagnetic, or other magnetic-sensitive metals implanted in their head within 30 cm of the treatment coil. Examples include cochlear implants, implanted electrodes/stimulators, aneurysm clips or coils, stents, bullet fragments, jewelry and hair barrettes. Failure to follow this restriction could result in serious injury or death. The NeuroStar TMS Therapy System and MagStim BiStim TMS system is contraindicated for use in patients who have active or inactive implants (including device leads), including deep brain stimulators, cochlear implants, and vagus nerve stimulators. Contraindicated use could result in serious injury or death. To avoid these complications, participants with any of the above listed implanted objects will be excluded from this study.

Childbearing Potential- There may be unknown risks to the fetus. Therefore, women of childbearing age will complete a pregnancy test for the TMS portion of the study at each visit. In order for the women of childbearing age to participate in this study, the

participant should avoid becoming pregnant from their first day of most recent menses. A negative pregnancy test does not absolutely prove that a woman is not pregnant. If the female participant thinks that there is a possibility that she might be pregnant, the study team should be notified immediately. Nursing mothers are not eligible for participation in this project. The possibility exists that complications and undesirable side effects, which are unknown at this time, could occur.

EEG:

A gel paste is used to attach the sensors during EEG which may mildly and briefly irritate the skin on the scalp or face. Hair products cannot be used on the day of testing (or should be washed out prior to testing), which may be inconvenient to the participant.

Some questionnaires ask questions of a personal nature and may cause feelings of discomfort or sadness. You may always choose to skip questions, take breaks as needed, and stop questioning at any time if you experience this kind of discomfort. We also ask questions about suicide which may be uncomfortable or bring up feelings of sadness. If there is evidence for significant major depression or suicidal ideation on the survey assessment, we will make a referral for psychiatric care or counseling as needed.

This Research Study may also include risks that are unknown at this time.

Please note, participating in more than one research study or project may further increase the risks to you. If you are already enrolled in a research study, please inform one of the Research Team members listed in question 3 of this form or the person reviewing this consent with you before enrolling in this or any other research study or project.

During the study, the Research Team will notify you of new information that may become available and might affect your decision to remain in the study.

The University of Florida is required by law to protect your health information. Your health information will be stored in locked filing cabinets or on computer servers with secure passwords, or encrypted electronic storage devices, as required by University policy. However, there is a slight risk that information about you could be released inappropriately or accidentally. Depending on the type of information, a release could upset or embarrass you, or possibly affect your ability to get insurance or a job.

If you wish to discuss the information above or any discomforts you may experience, please ask questions now or call one of the Research Team members listed in question 3 in this form.

13a. What are the potential benefits to you for taking part in this Research Study?

You may or may not benefit from taking part in this study. All participants will experience both real rTMS and sham rTMS in random order. Real rTMS may improve the length of time that botox is effective or may lead to a more robust improvement in your cervical dystonia. The rTMS may also help with mood, cognition, and walking.

13b. How could others possibly benefit from this Research Study?

The information gathered from this study will benefit the neurology department and the larger research community as we continue to seek the most efficacious treatments for cervical dystonia. The information from this study will be used to help improve treatments for cervical dystonia and associated conditions such as depression, walking difficulties, and cognitive (memory or thinking) changes. We will also use the data collected form this study to help understand the underlying mechanism of cervical dystonia, which could lead to further treatment developments in the future.

13c. How could the Research Team members benefit from this Research Study?

In general, presenting research results helps the career of a researcher. Therefore, the Research Team listed in question 3 of this form may benefit if the results of this Research Study are presented at scientific meetings or in scientific journals.

13d. Will you be allowed to see the research information collected about you for this Research Study?

You may not be allowed to see the research information collected about you for this Research Study, including the research information in your medical record, until after the study is completed. When this Research Study is over, you will be allowed to see any research information collected and placed in your medical record.

14. What other choices do you have if you do not want to be in this study?

This study is completely voluntary. You may discuss treatment options with your regular neurologist.

You may also refuse to authorize the use of your health information, but if you refuse, you may not be allowed to be in this research study or receive any research-related treatment that is only available in this research study. However, your decision not to sign this Authorization will not affect any other treatment you may be eligible to receive.

15a. Can you withdraw from this study?

You may withdraw your consent and stop participating in this Research Study at any time. If you do withdraw your consent, there will be no penalty to you, and you will not lose any benefits to which you are otherwise entitled.

If you decide to withdraw your consent to participate in this Research Study for any reason, please contact the Research Team listed in question 3 of this form. They will tell you how to safely stop your participation.

You can also change your mind and take back this Authorization at any time by sending a written notice to the Research Team listed in question 3 of this form to let them know your decision. If you take back this Authorization, the Research Team may only use and disclose your health information already collected for this research

study. No additional health information about you will be collected or disclosed to the Research Team. However, if you take back this Authorization, you may not be able to continue in this study. Please discuss this with a member of the Research Team listed in question #3.

15b. Can the Principal Investigator withdraw you from this Research Study?

You may be withdrawn from this Research Study without your consent for the following reasons:

- The Principal Investigator believes the study is not in your best interest
- The study is ended early
- If you have a seizure
- If you become pregnant

WHAT ARE THE FINANCIAL ISSUES IF YOU PARTICIPATE?

16. If you choose to take part in this Research Study, will it cost you anything?

No. There will be no extra cost to you for participating in this Research Study.

17. Will you be paid for taking part in this Research Study?

You will be compensated for the following items in the form of gift cards:

-if you live a minimum of 50 miles from Gainesville, you will be offered a 4-night hotel stay of up to $100 per night in Gainesville for 4 nights so that you can complete the 4 consecutive days of rTMS. You will receive $400 for your first hotel stay during week 9 and another $400 during your second hotel stay during week 21.
-You will receive up to $150 for gas/travel expenses and will be provided with $25 during each of your 6 visits to the Fixel Center/UF
-You will receive up to $150 for food expenses and will be provided with $25 during each of your 6 visits to the Fixel Center/UF
-You will receive up to $150 for compensation of your time for participating in this study and will be provided with $25 during each of your 6 visits to the Fixel Center/UF

If you are paid more than $75 for taking part in this study, your name and social security number will be reported to the appropriate University employees for purposes of making and recording the payment as required by law. You are responsible for paying income taxes on any payments provided by the study. Payments to ***nonresident aliens*** must be processed through the University of Florida Payroll and Tax Services department. If the payments total $600 or more in a calendar year, the University must report the amount you received to the Internal Revenue Service (IRS). The IRS is not provided with the study name or its purpose. If you have questions about the collection and use of your Social Security Number, please visit: http://privacy.ufl.edu/SSNPrivacy.html.

Your payment for participation in this research study is handled through the University of Florida's Human Subject Payment (HSP) Program. Your information which will include your name, address, date of birth, and SSN (depending on amount of money you are paid) is protected. Access to the (HSP) Program site is limited to certain staff with the assigned security role. You will be randomly assigned a specific identification (ID) number to protect your identity.

If you have any problems regarding your payment contact the study coordinator.

18. What if you are injured while in this Research Study?

If you are injured as a direct result of your participation in this study, only the professional services that you receive from any University of Florida Health Science Center healthcare provider will be provided without charge. These healthcare providers include physicians, physician assistants, nurse practitioners, dentists or psychologists. Any other expenses, including Shands hospital expenses, will be billed to you or your insurance provider.

You will be responsible for any deductible, co-insurance, or co-payments. Some insurance companies may not cover costs associated with research studies or research-related injuries. Please contact your insurance company for additional information.

The Principal Investigator will determine whether your injury is related to your participation in this study.

No additional compensation is routinely offered. The Principal Investigator and others involved in this study may be University of Florida employees. As employees of the University, they are protected under state law, which limits financial recovery for negligence.

Please contact the Principal Investigator listed in question 3 of this form if you experience an injury or have questions about any discomforts that you experience while participating in this study.

Consent to be Photographed, Video and/or Audio Recorded

With your permission, you will have the following done during this research (check all that apply):

☐ photographed ☐ video recorded ☐ audio recorded

Your name or personal information will not be identified on the photograph(s), video or audio recordings, and confidentiality will be strictly maintained. However, when these photograph(s), video and/ or audio recordings are shown or heard, others may be able to identify you.

The Principal Investigator (PI) of this study, _____, or *[his/her]* successor, will keep the photograph(s), video and/or audio recordings in a locked cabinet, in a folder on a password protected computer server drive, or as an encrypted electronic file. These photograph(s), video and/or audio recordings will be shown under *[his/her]* direction to students, researchers, doctors, or other professionals and persons. Please indicate under what conditions Dr. _____ has your permission to use the photograph(s), video and/or audio recordings, and sign and date below.

☐ The following will be **destroyed once the study is closed** (initial next to all that apply):

____ photograph(s) _____ video recording(s) _____ audio recording(s)

☐ As described in the Informed Consent Form, and for the purposes of **education at the University of Florida Health Science Center**. The PI may keep the following for an indefinite period of time in a locked file, in a password protected computer server drive, or as an encrypted electronic file (initial next to all that apply):

____ photograph(s) _____ video recording(s) _____ audio recording(s)

☐ As described in the Informed Consent Form; for the purposes of **education at the University of Florida Health Science Center; and for presentations at scientific meetings outside the University**. The PI may keep the following for an indefinite period of time in a locked file, in a password protected computer server drive, or as an encrypted electronic file (initial next to all that apply):

____ photograph(s) _____ video recording(s) _____ audio recording(s)

_____ _____

Signature Date

SIGNATURES

As an investigator or the investigator's representative, I have explained to the participant the purpose, the procedures, the possible benefits, and the risks of this Research Study; the alternative to being in the study; and how the participant's protected health information will be collected, used, and shared with others:

Signature of Person Obtaining Consent and Authorization	Date

You have been informed about this study's purpose, procedures, possible benefits, and risks; the alternatives to being in the study; and how your protected health information will be collected, used and shared with others. You have received a copy of this Form. You have been given the opportunity to ask questions before you sign, and you have been told that you can ask questions at any time.

You voluntarily agree to participate in this study. You hereby authorize the collection, use and sharing of your protected health information as described above. By signing this form, you are not waiving any of your legal rights.

Signature of Person Consenting and Authorizing	Date