Mixed Methods Investigation of Chronic Facial Paralysis in Individuals with Synkinesis: Study of Outcomes Before and After Treatment
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Mixed Methods Investigation of Chronic Facial Paralysis in Individuals with Synkinesis: Study of Outcomes Before and After Treatment

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Summary

Facial nerve paralysis is a devastating event that in up to 30% of cases may result in chronic weakness and/or the disfiguring condition of synkinesis, a long-lasting muscle discoordination of facial movement caused by aberrant facial nerve regeneration after facial nerve paralysis. This is believed to have a detrimental effect on social interactions, mental health, and quality of life.

Neuromuscular retraining therapy and ipsilateral chemodenervation into discoordinated muscles by injection (onabotulinumtoxinA/Botox, Allergan or incobotulinumtoxinA/Xeomin, Merz) are two common treatments for the abnormal muscle movements found in synkinesis. No study has compared the effectiveness of these treatment modalities for synkinesis. Retrospective data including our series at the University of Wisconsin *Facial Nerve Clinic* show significant benefit of retraining therapy using clinician- and patient-reported outcome measures. However, the manner in which this therapy may be optimized for use in treatment of the sequelae of facial paralysis is unclear. While literature shows beneficial improvement in outcomes with chemodenervation in prospective studies, no study has explored the effectiveness of physical therapy for synkinesis in a controlled, prospective manner. Further, the efficacy of therapy has not been shown to improve recognition and emotional information interpretation, both thought to be impaired in synkinesis.

This proposal will prospectively assess the social, physical, and emotional recognition function in patients with synkinesis. Next, it will measure the effectiveness of neuromuscular retraining therapy to improve muscle coordination compared to chemodenervation, the more established treatment modality, in a single-blinded, randomized control trial using clinician- and patient-reported outcomes measures. Our hypothesis is that patients undergoing neuromuscular retraining therapy will achieve greater improvement on clinical outcome measures as compared to patients receiving chemodenervation.

In this clinical trial, 36 patients undergoing treatment for synkinesis will be enrolled into one of two treatment arms: chemodenervation or neuromuscular retraining therapy. There are 3 specific aims:

AIM 1: Determine the effect of neuromuscular retraining or chemodenervation on clinician-reported and patient-reported outcomes. The primary outcome measure after four and eight months of treatment will be the clinician-reported Sunnybrook Facial Grading System (SFGS) scored on patient videos by blinded reviewers. Further, we seek to measure the efficacy of treatment with existing patient-reported instruments. We will calculate the correlation of clinician-reported outcome measure changes to changes in patient-reported instruments with treatment, including the widely utilized disease specific Synkinesis Assessment Questionnaire (SAQ) and Facial Clinimetric Evaluation Scale (FaCE), and with two disease non-specific instruments, the Hospital Anxiety and Depression Scale (HADS), and Brief-Illness Perception Questionnaire (BIPQ). We will also measure the efficacy of our clinical intervention with social-perceptual and mental health outcome measurement before and after treatment (AIM 3).

AIM 2: Determine the social, emotional, and functional burden of synkinesis, not captured in current patient-reported outcome measures as well as effect of treatment. We will analyze qualitative interviews with individual patients collected before treatment, after four of treatment, and after eight months of treatment to study the burden of disease, experience with treatment, and potential differences in both treatments. Our primary outcome is to identify the domains that may be missing from existing patient-reported measures collected in AIM 1. To do this, we will compare findings to assessment domains (i.e. decreased engagement, negative mood, etc.) in the FaCE, SAQ, and the two disease non-specific instruments, HADS and BIPQ. We will then evaluate our findings based on domains in PROMIS measures, an NIH-supported collection of validated and standardized scales.

AIM 3: Quantify the disruption in social functioning caused by synkinesis using innovative social-perceptual outcomes and emotion recognition tasks. Prior to treatment, participants will enroll in IRB Protocol 2015-0366 and complete a series of social functioning and mental health instruments and emotion expression recognition tasks. Results will be compared to control subjects without facial disability to reveal the social-perceptual impairment attributable to synkinesis. Repetition of these tasks after four months of either treatment may show improvement in recognition and emotional information interpretation when compared to initial measurements.

Figure 1: Trial overview diagram

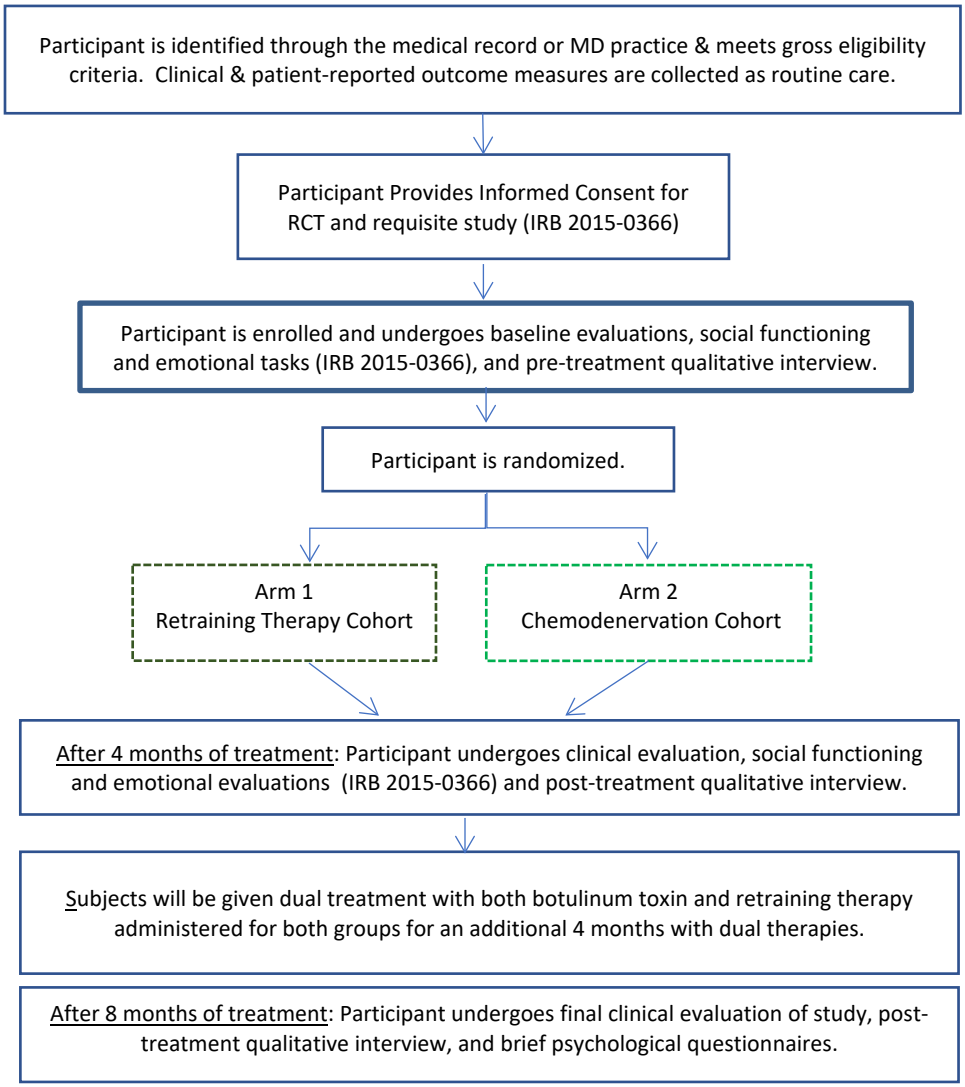
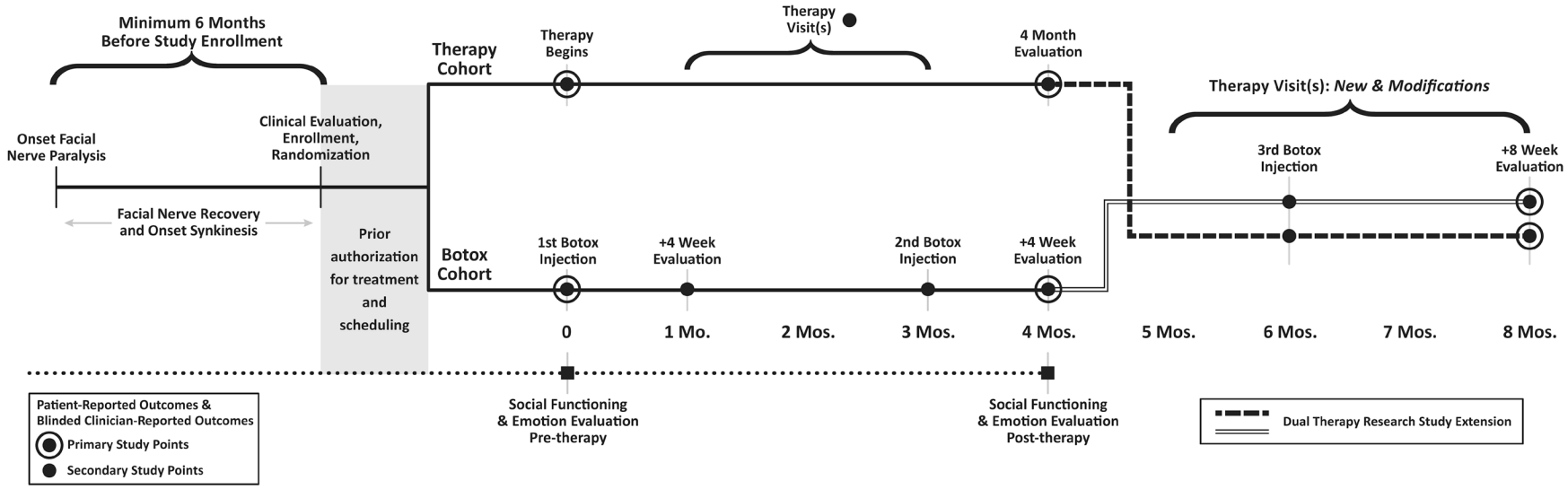


Table 1. Schedule of activities

	Pre-treatment	Phase I	Study midpoint	Phase II	Study concludes
	Screening	Therapy or chemodenervation per standard protocol	4-month evaluation	Pragmatic trial with dual therapies	8-month evaluation
Window	>6 weeks after onset of paralysis-24 hours before treatment	Routine visits over four months	After four months	Routine visits over next four months	After four months of dual therapy
Informed Consent Obtained	X				
Randomization	X				
Enrolled	X				
Clinical Evaluation	SOC	SOC	SOC	SOC	SOC
Interviews (Audio Recorded)	X		X		X
Adverse Events Monitoring	X		X		X
Assessment of Facial Movement, Paralysis & Well-Being					
Facial Clinimetric Evaluation (FaCE) Scale (10 min)	SOC	SOC	SOC	SOC	SOC
Sunnybrook Facial Grading System (SFGS) [Video]	SOC	SOC	SOC	SOC	SOC
Synkinesis Assessment Questionnaire (SAQ) (10 min)	SOC	SOC	SOC	SOC	SOC
Psychological Assessments (HADS, BIPQ) (15 min)	E		E		X
Social Functioning and Emotion Evaluation Tasks (Protocol 2015-0366)					
Emotion Recognition Tasks (37 min)	E		E		
Risk Perception and Decision Making Tasks (45 min)	E		E		

Procedure Key: **SOC** = performed as needed per Standard of Care; **X** = Research Only, for this protocol; **E** = Research Only, for IRB Protocol 2015-0366

Figure 2. Diagram of activities



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List of abbreviations and definitions

AE	Adverse event
BIPQ	Brief-Illness Perception Questionnaire
DMC	Data Monitoring Committee
eCRF	Electronic case report form
EDC	Electronic data capture
FaCE	Facial Clinimetric Evaluation
HADS	Hospital Anxiety and Depression Scale
IRB	The institutional review board of record for the study
SAQ	Synkinesis Assessment Questionnaire
SFGS	Sunnybrook Facial Grading System
SOC	Standard of care
UW	University of Wisconsin

1. Introduction

1.1. Background

Bell's Palsy is an idiopathic peripheral facial nerve disorder that results in unilateral weakness or paralysis, afflicting 11.5 to 53.3 patients per 100,000.[1] While many patients show complete recovery by three months, up to 30% will have persistent symptoms that could include chronic paralysis, chronic paresis (weakness) and/or synkinesis.[2] The University of Wisconsin *Facial Nerve Clinic* is a regional multi-disciplinary clinic that treats patients with these sequelae of peripheral facial nerve injury. While Bell's palsy is the most common cause of facial paralysis, these sequalae can occur after any cause of peripheral facial nerve paralysis including acoustic tumor surgery, Lyme disease, and many others. Approximately 1,700 patients will receive a Bell's palsy diagnosis each year in Wisconsin, leaving up to 500 patients with symptoms such as chronic weakness or synkinesis after Bell's palsy alone.

Synkinesis is a chronic clinical condition that causes distressing involuntary facial movement resulting from aberrant neural regeneration after peripheral facial nerve injury.[3] It generates both hypertonicity of recovered facial muscles and also involuntary, discoordinated facial movements that may significantly interfere with facial functions such as blinking, chewing, speaking, smiling, and nasal breathing. The proposed work addresses substantial gaps in knowledge that limit effective clinical care of patients with aberrant recovery after all causes of peripheral facial nerve paralysis.

Neuromuscular retraining therapy and chemodenervation injection into the affected, ipsilateral, muscles (onabotulinumtoxinA/Botox, Allergan or incobotulinumtoxinA/Xeomin, Merz) are two common treatments for synkinesis.

Neuromuscular retraining is a type of physical therapy that strives to improve coordination among synkinetic facial muscles by enhancing neural adaptation and motor learning. Therapy is a comprehensive program that includes patient education, sensory feedback (including surface electromyography, proprioceptive and mirror feedback), and at home practice of minimal, precisely coordinated movements. The goal of neuromuscular retraining is to improve motor patterns in much the same way as learning to play piano or other fine motor skill, through individualized home daily practice. It is distinguished from non-specific therapies in that it does not use gross motor, maximum effort exercises or electrical stimulation, which can reinforce abnormal movement patterns. A seminal controlled trial in 1991 showed that neuromuscular retraining, which includes monthly retraining visits and a structured home rehabilitation program, was efficacious in a small group of patients with long-standing synkinesis. More recently, therapy was shown to decrease oral synkinesis stimulated by brow or ocular motion in an uncontrolled cohort study.

Our team recently completed a retrospective cohort analysis of 53 consecutive facial synkinesis patients seen at the UW *Facial Nerve Clinic* from 2012-2016, with a cohort evaluated at least 4 months after onset of paralysis to the first therapeutic encounter and in patients who underwent at least 3 months of retraining therapy. The patient-reported Synkinesis Assessment Questionnaire (SAQ) and clinician-reported Sunnybrook Facial Grading System (SFGS) were administered before and after therapy finding a small mean improvement (and large variation) on the patient-reported SAQ of 3.9 (SD 24.0, p=0.25) from baseline SAQ score 64.4 (IQR 46.7-80.0). However, our UW team of clinicians recorded clinically and statistically significant mean improvement of 9.4 (SD=7.1, p <0.001) from baseline SFGS score 53.0 (IQR=47.0-67.0). While these retrospective data are subject to bias, the trends support our hypothesis that neuromuscular retraining therapy is efficacious for the treatment of synkinesis on the clinician-reported SFGS. The data also supported a secondary hypothesis that our current patient-reported instrument does not adequately capture the patient condition before or after treatment.

Chemodenervation selectively weakens discoordinated muscles seen in synkinesis temporarily, and has been shown to improve outcome measures in both retrospective and prospective trials. It has been described as a gold standard for synkinesis after peripheral facial paralysis to temporarily denervate facial muscles with three controlled trials in the Cochrane central register. First, Borodic demonstrated improvement in multiple aspects of quality of life with botulinum toxin injections using author-generated, patient-reported outcome instruments compared to saline injection in a double-blinded controlled trial; improvement was also seen with an author-generated synkinesis grading scale. In the second study, Nascimento evaluated injections on the non-paralyzed side of face, a treatment that improves symmetry (e.g. eyebrow position) but does not address hypertonicity and involuntary, discoordinated facial movements. Third, Monini found ipsilateral chemodenervation combined with neuromuscular retraining therapy showed greater improvement on the clinician-reported Sunnybrook Facial Grading System (SFGS) than with therapy alone, however therapy was provided at an unspecified frequency for unspecified length of time.

No study has compared the effectiveness of these two treatment modalities for synkinesis, or prospectively evaluated neuromuscular retraining therapy as single or combined modalities. Indeed, the efficacy of physical therapy treatment modalities has been cited as a research gap in clinical practice guidelines. Many studies have investigated therapy during early months of facial paralysis, failing to control for spontaneous muscle recovery or simply before the onset of synkinesis.[1, 4] Other studies, including the large series at the Massachusetts Eye and Ear Infirmary Facial Nerve Center,[5] evaluated efficacy of therapy confounded by chemodenervation, which was performed simultaneous to retraining therapy. A more recent study of patients with peripheral facial nerve injury compared chemodenervation to a control group which received adhesive plaster traction to pull skin to prevent paretic muscles from stretching; however, therapy was introduced in both groups, again confounding the efficacy of each therapy.[6]

We will conduct a prospective, randomized, single-blinded control trial of neuromuscular retraining therapy versus patient receipt of chemodenervation. Both treatments are widely practiced in the United States for the treatment of synkinesis, and it is not known if retraining therapy achieves better clinical outcomes as compared to chemodenervation. The study design allows measurement of improvement attributable to each treatment and reduces bias through randomization to each study arm. A video-based single-blinded scoring of outcome measures also reduces bias. The first four months of the protocol will allow comparison of individual treatments to answer this research question; the next four months of the protocol will measure additional changes with dual treatment while patients received both therapies in a pragmatic trial emulating clinical practice.

1.2. Rationale and hypothesis

We propose a clinical trial in which 36 patients with synkinesis will be enrolled into one of two treatment arms: chemodenervation alone followed by dual therapy (i.e. add neuromuscular retraining), and neuromuscular retraining alone followed by dual therapy (i.e. with chemodenervation). In the absence of this clinical trial, patients seen at our center would be offered one or both treatments based on clinician judgment and patient preference, which is our current practice standard. At other major academic centers, however, chemodenervation may be the standard of care due to provider preference, training, or the lack of qualified retraining therapist. While many institutions use chemodenervation monotherapy routinely in their practice, high volume centers that publish research data on facial paralysis report both techniques. There is no published consensus or written guidelines on the treatment of synkinesis including choice of treatment, sequence of treatment, and timing to add dual

therapy. We hypothesize clinician-reported outcome measures will show statistically greater improvements for retraining therapy as compared to chemodenervation.

Chemodenervation has a rapid onset and has been shown to improve patient-reported outcomes; however, the effect is temporary usually requiring re-injection every three to four months as is the case with all conditions treated with injections. In contrast, neuromuscular retraining provides long lasting improved coordination among synkinetic facial muscles, but often does not provide patients with complete resolution of symptoms. Selective ipsilateral chemodenervation of synkinetic muscles can be used in conjunction with neuromuscular retraining therapy to provide a window of opportunity, in which the patient learns to practice isolated, coordinated movements without the co-contraction and restriction caused by synkinesis. While combined chemodenervation and therapy may result in optimal treatment, the efficacy, timing, and sequence of dual treatment still needs to be elucidated for patients with synkinesis.

In the first four months of the trial, we hypothesize that patients undergoing neuromuscular retraining therapy will achieve statistically greater improvements on clinician-reported outcome measures as compared to patients receiving chemodenervation. Patients may achieve the additional gains after combined treatments duringn the next four months of the trial. There may exist interesting differences in our secondary data collection of patient-reported measures and interview data after single and dual treatments.

2. Objectives

2.1. Primary outcome and endpoints

To determine improvement in physical functioning from baseline, we will look at the change on the clinician-reported Sunnybrook Facial Grading System (SFGS). The examination is routinely collected at clinic visits. At each clinic visit, patients will be videotaped as a part of routine care. However, patients in the study will undergo a blinded evaluation and SGFS scoring using the video by trained blinded clinicians not participating in their direct clinical care, to decrease observer bias.

2.2. Secondary outcomes and endpoints

To determine the physical/functional, social, and emotional burden of synkinesis and efficacy of treatment, qualitative analyses of patient interview data and patient-reported instruments will be used to assess the impact of synkinesis on patient's lives.

- SAQ and FaCE scores (disease specific patient-reported instruments routinely collected as part of clinical care)
- HADS and BIPQ scores (depression, anxiety, and illness perception patient-reported instruments)
- Themes, codes from interview transcripts (using qualitative research methods)

Interviews and SAQ and FaCE scores will be collected before treatment, after four months of treatment, and after eight months of treatment.

The HADS and BIPQ mental health instruments will be collected before and repeated after four months of treatment (as part of participation in Protocol 2015-0366) and eight months of treatment (as part of participation in this protocol).

To quantify the disruption in social functioning caused by synkinesis, participants will enroll in IRB Protocol 2015-0366 and complete a series of social functioning and mental health instruments, and emotion expression recognition tasks. Repetition of emotional expression recognition tasks after four

months of treatment may show improvement in recognition and emotional information interpretation; these tasks will not be repeated after eight months as no meaningful or statistical difference is anticipated at this time point.

SFGS, SAQ, and FaCE are all part of the standard treatment and follow up of patients with synkinesis. The only activities that will be conducted for research purposes are the qualitative interviews, the tasks in Protocol 2015-0366 (done before treatment and after four months of treatment, which include the HADS and BIPQ), and the HADS and BIPQ after 8 months of treatment (this protocol).

3. Study design

This study will compare chemodenervation with neuromuscular retraining. Both treatments are widely practiced in the United States for the treatment of synkinesis, and it is not known which is best.

Participant Identification and Eligibility:
Participants will be primarily identified from our University of Wisconsin *Facial Nerve Clinic*. While most patients with facial nerve paralysis recover in 3 months, patients with chronic facial paralysis may still benefit from spontaneous recovery of muscle function thereafter. Symptoms of synkinesis are often not displayed until 4 months with the display of aberrant facial muscle motions. Eligible patients will demonstrate synkinesis and had their onset of peripheral facial paralysis from any cause at least 4 months prior. Muscle function and synkinesis will be assessed using standard clinical evaluation tools.

Exclusion criteria: (1) under 18 years of age (2) previous treatment with reanimation surgery (except for those patients who underwent upper eyelid weight placement to aid in eye closure), (3) intolerance or contraindication to botulinum toxin injection, and/or (4) previous treatment for synkinesis with chemodenervation or neuromuscular retraining therapy (5) vulnerable populations such as known prisoners, pregnant/breastfeeding women, or subjects with impaired decision-making capacity, including those with severe psychiatric illnesses (6) individuals over 89 years of age

Pre-Treatment Screening and Testing: Pre-treatment activities will include clinical evaluation and clinician- and patient-reported instruments that are already standard of care (SFGS, SAQ, FaCE), a semi-structured interview, and the tasks included in IRB Protocol 2015-0366. Patients will be randomly assigned to one of two treatments; Arm 1: neuromuscular retraining therapy for four months, with chemodenervation added thereafter, or Arm 2: Botox/chemodenervation for four months, with neuromuscular retraining therapy added thereafter. Allocation schedule will not be known to clinicians prior to consenting.

Blinding: Research team members who will score the videos will be blinded. The physician conducting the initial clinic visit will be blinded to the patient's treatment arm until after they have been enrolled. The physician providing treatment, interviewer, and study coordinator will not be blinded to the participant's treatment arm.

Treatment and follow-up: Treatment will be performed using standard techniques in all patients. All patients will be followed by providers approximately once per month for either neuromuscular retraining therapy or botulinum toxin injection/injection evaluation over the phone, per routine clinical care. Follow-ups will provide preliminary data on treatment outcomes. Patients will also complete the SAQ and FaCE at each visit, and one month after chemodenervation as per routine protocol. Patients will undergo interviews (and tasks entailed in IRB Protocol 2015-0366) after 4 months of treatment, to determine the effects (if any) of treatment on physical, social, and emotional burden.

Patients will undergo dual therapy for four months after the initial four months. They will continue to complete the SAQ and FaCE at each care visit and will be asked to complete a qualitative interview and BIPQ and HADS instruments after 8 months of treatment.

It can be difficult to coordinate interviews with regularly scheduled patient visits. If the study team is unable to schedule these procedures on the same day, the subject will be given the option of returning on a different day of their choosing. If there are extenuating circumstances, the subject may complete the interview over the phone or via video conferencing software called WebEx. The research-only evaluations do not affect clinical care for patients.

At each time point (pre-treatment, after 4 months of treatment, and after 8 months of treatment), a trained interviewer who is not a member of the clinical staff will conduct a semi-structured qualitative interview. We will invite everyone to interview, with the goal of at least 24 patients completing interviews before treatment and after 4 months of treatment. The interview at 8 months will be optional. Interview guides were developed in consultation with clinical staff and piloted prior to use; guides include both prompted and unprompted open-ended questions aimed at understanding patient experience with various aspects of synkinesis and treatment. All interviews will be transcribed verbatim and any identifiers will be removed from transcripts prior to coding. Data will be coded using a catalogue of codes developed through analysis of emergent themes in a subset of interview transcripts. The Qualitative Core in the Wisconsin Surgical Outcomes Research Program will assist with data collection and analysis associated with qualitative aims.

The interview recordings will be transcribed by trained transcriptionists employed through the Wisconsin Surgical Outcomes Research Program (WiSOR) or an outside contractor with a business associate agreement that has been approved by UW Legal Services/Privacy Officer for HIPAA compliance. Transcriptionists have been instructed to remove identifying information from the transcripts. The audio recordings and transcripts will be shared through a secure server that only the transcriptionists and study team members have access to.

The completed interview transcripts will be stored on the secure network within the Wisconsin Surgical Outcomes Research Program (WiSOR). The main levels of security for this data application server housed at the SMPH Computer Center include being securely located behind the UW-Madison campus firewall, having data directory access controls, having physical server security, and having virtual server security. The participants' names and identifying information will be stored separately from the interview transcripts. The only link between the transcripts and the identifying information will be a subject identification number contained in both data files.

4. Study population

4.1. Inclusion criteria

Each patient must meet all of the following inclusion criteria to be enrolled in the study.

1. Has ipsilateral synkinesis of facial muscles
2. It has been at least four months since their onset of peripheral facial paralysis from any cause
3. Age 18 or older
4. Ability to read and write in English

4.2. Exclusion criteria

Patients meeting any of the following exclusion criteria are not to be enrolled in the study.

1. Under 18 years of age
2. Previous treatment with reanimation surgery (except for upper eyelid weight placement)
3. Intolerance or contraindication to botulinum toxin injection
4. Previous treatment for synkinesis with chemodenervation or neuromuscular retraining therapy
5. Pregnant and/or breastfeeding women
6. Patients with impaired decision-making capacity, including those with severe psychiatric illnesses
7. Individuals over 89 years of age

4.3. Protected populations

We will not be including any vulnerable populations, such as children, prisoners, those without decision making capacity or women known to be pregnant in this study.

5. Trial interventions

The intervention portion of this study is the assignment to Treatment Arm 1 or Treatment Arm 2.

5.1. Treatment Arm 1 (Neuromuscular retraining therapy)

Neuromuscular retraining therapy alone for four months, with botulinum toxin injection added during an additional four month period.

5.2. Treatment Arm 2 (Chemodenervation)

Ipsilateral chemodenervation with botulinum toxin injections alone for four months (onabotulinumtoxinA/Botox, Allergan or incobotulinumtoxinA/Xeomin, Merz), with neuromuscular retraining therapy added for an additional four months. Prior authorization for therapy will be done through normal clinical protocols as routine patient care.

OnabotulinumtoxinA/Botox is the preferential choice of neurotoxin, unless this is not allowed by the patient's insurance carrier in which case incobotulinumtoxinA/Xeomin will be utilized. The UW Pharmacy and Therapeutics Committee has evaluated the two and determined them to be equivalent for this and other treatments. Prior authorization for drug injection will be done through normal clinical protocols as routine patient care.

5.3. Allocation to intervention

Participants will be randomized to each treatment arm with equal probability (1:1 randomization) using a computerized random number generator with random block size (all study personnel except the statisticians are blinded to block size). The randomization assignment will be revealed to the unblinded study coordinator after consent. The clinicians will be blinded to the treatment until the end of clinic.

6. Participant recruitment and consent

6.1. Participant identification

We will recruit patients from the University of Wisconsin *Facial Nerve Clinic.*

6.2. Screening

UW Health physicians who treat facial nerve disorders, will assess patient eligibility. Departments of Surgery, Otolaryngology, Neurosurgery, and Neurology and therapists in the Department of Orthopedics and Rehabilitation, will identify patients who meet the study requirements. All protected health information used during the screening process of a potential participant will be the minimum necessary for the conduct of this study. Any protected information recorded will be destroyed at the end of the

screening process unless the patient enrolls. The clinical care team of the potential participant will be aware of the potential participation in this study as they will be the ones who refer the participant.

6.3. Recruitment and consent

The human subjects participating in this study will be recruited from the University of Wisconsin *Facial Nerve Clinic*. After physicians identify eligible patients and introduce available treatments, they will ask if the patient is interested in speaking to a study coordinator. A study coordinator will then offer enrollment in both IRB protocol 2015-0366 and this protocol. In clinics where the study coordinator is not available, patients will be given an information sheet, flowchart, and consent form describing the study during the patient's visit at UWHC and told that the coordinator will call within the week to explain the study.

A participant's decision whether or not to participate will not affect the care received as a patient. Participants will be treated according to the standard of care until consent for the study is obtained. Participants must meet inclusion and exclusion criteria as listed above. Participants will be selected without consideration of socio-economic background, however if their insurance status precludes them from coverage for therapy and/or Botox they will need to pay out of pocket. If they are unwilling/unable to do this, we will not to enroll them in the study as their treatment with only the treatment covered by insurance would not be truly random.

Following explanation of the consent form, each potential participant will be given an opportunity to read it thoroughly. Before being allowed to sign the consent form, potential participants also will be given an opportunity to ask questions. The investigator will emphasize the fact that the participant can terminate involvement at any time without any consequences. Once the consent form has been signed, the study pre-treatment procedures will be performed if not already captured in the medical record.

A participant is enrolled prior to treatment and will undergo baseline evaluations. They will be randomized on the day of their initial clinic visit.

6.4. Compensation

We will provide $25 for each semi-structured interview before treatment, after four months, and after eight months of treatment for a potential total of $75. This is in addition to compensation for completion of tasks of protocol 2015-0366 which are $25 for emotion testing before treatment and again after four months.

7. Activities and measurements

Enrollment: Participants will be enrolled after signing the informed consent form.

Pre-treatment visit: During the initial visit, the multi-disciplinary clinical team (therapist and surgeon) will provide education on eye care and avoidance of other therapies that could worsen the synkinesis before treatment is initiated (e.g. maximal effort exercises), and describe treatment with neuromuscular retraining therapy and chemodenervation with botulinum toxin injections. Both treatments are standards of care and will be presented without bias as options. After the clinical evaluation, the Study Coordinator will offer study enrollment, obtain consent and assign cohort based on randomization. We will use a predetermined and blind randomization sequence designed independently by the study biostatistician.

The pre-treatment visit will include a baseline assessment of every participant's facial function and patient-reported instruments, per standard of care. The pre-treatment interview and completion of tasks entailed in IRB Protocol 2015-0366 may be conducted on the same day or scheduled for later at the subject's convenience.

Treatment: Once the patient enrolls, the participant will be informed of the treatment to which they were randomized. Study arm randomization will be computer generated by study biostatistician, Dr. Bret Hanlon.

- Treatment Arm A: Therapy cohort participants will be scheduled for neuromuscular retraining therapy, with treatment provided per routine clinical care and additional home therapy program as directed. Patients will have at least two neuromuscular retraining therapy sessions as determined by the therapist and patient per routine clinical practice, each about 4-8 weeks apart
- Treatment Arm B: Chemodenervation cohort participants will undergo injection with ipsilateral botulinum toxin at 0 months as determined by common clinical practice, and a second injection 3 months later with modifications based on patient feedback, again by common clinical practice. Patients will have a follow-up evaluation one month after each injection, often done by phone
- At each clinic visit, patients will be videotaped performing standard 11-view photography and 7-position videography, a standard clinical protocol recommended for all facial nerve centers. The clinician documents and score the Sunnybrook Facial Grading System (SFGS) in the chart. After the clinic visits, blinded observers on the study team will also view the photography and videography to blindly score the SFGS clinician-reported outcome measure at 0, 4, and 8 months.

Four-month visit: Both groups will return at 4 months to participate in a qualitative interview and the tasks outlined in IRB Protocol 2015-0366. If there are extenuating circumstances, subjects will be able to complete the four-month visit over video conferencing software with Vidyo. Evaluations will be performed per standard of care. No clinical intervention will be made at the 4-month visit. Patients may elect to exit the study at this phase. Subjects who continue the study will then be given dual treatment, with chemodenervation administered for both groups for an additional 4 months and Arm B participants starting neuromuscular retraining therapy, in a pragmatic trial with dual therapies.

Eight-month visit: Patients will return at 8 months to fill out the BIPQ and HADS and participate in a qualitative interview. If there are extenuating circumstances, subjects will be able to complete the four-month visit over video conferencing software with Vidyo. No clinical intervention will be made at the 8-month visit.

Time required for study procedures: Standard clinic visit for photos & video, clinical evaluation & patient-reported instruments
60-90 minutes for qualitative interview
1-2 hours for tasks in IRB Protocol 2015-0366
10 minutes for BIPQ and HADS

7.1. Table: Time points for data collection

	Pre-treatment	Phase I	Study midpoint	Phase II	Study concludes
	Screening	Therapy or chemodenervation	4-month evaluation	Pragmatic trial with dual therapies	8-month evaluation

		per standard protocol			
Time Window	6 weeks-24 hours before treatment	Four months	After four months	Four months	After four months of dual therapy
Facial Clinimetric Evaluation (FaCE) Scale (10 min)	SOC	SOC	SOC	SOC	SOC
Sunnybrook Facial Grading System (SFGS)	SOC	SOC	SOC	SOC	SOC
Synkinesis Assessment Questionnaire (SAQ) (10 min)	SOC	SOC	SOC	SOC	SOC
Interviews (Audio Recorded) (60-90 min)	X		X		X
Psychological Assessments (HADS, BIPQ) (10 min)	E		E		X
Tasks from Protocol 2015-0366 (60-90 min)	E		E		

Procedure Key: **SOC** = performed as needed per Standard of Care; **X** = Research Only for this protocol; **E** = Research only for Protocol 2015-0366

7.2. Data entry

Data will be collected electronically. The following will be captured electronically: (1) data from the electronic medical record (see data collection sheet); (2) evaluation video and audio recordings and clinician reports/summaries; (3) audio recordings of participant interviews and electronic codes for content themes. Paper data collection may consist of the FaCE, SAQ, BIPQ, and HADS. Raw data will be scored or otherwise evaluated as necessary and entered into a REDCap database as soon as possible after data collection.

Video recordings collected during this study will not be immediately destroyed after all research procedures have been completed, as this data is collected as part of clinical care and could be of value to a follow up or related study. Subjects will have the opportunity to consent to their data being used in future studies. IRB approval will be sought for any use of this data outside of the study parameters described in this protocol.

7.3. Participant withdrawals

Participants have the right to withdraw from the study at any time for any reason, either before or after treatment begins. Additionally, any participant may be discontinued from the study at any time at the discretion of the investigator if he or another provider feels it is in the best interest of the participant. If a participant withdraws or is withdrawn from one aim, they may continue to participate in the other aims.

Study participation may be terminated early under the following circumstances:

(1) the participant does not meet all inclusion criteria and is deemed a screen failure
(2) the participant meets any of the exclusion criteria and is deemed a screen failure
(3) the participant does not adhere to protocol requirements (e.g., completing questionnaires, refusing permission to have interview recorded, etc.)
(4) the participant experiences an AE which in the investigator's opinion requires their withdrawal from the study
(5) the participant is lost to follow up
(6) death of the participant

The study team will document the reason(s) for withdrawal of each participant in source documents.

Participants that withdraw or are withdrawn prior to treatment will be replaced. Their pre-treatment data may be used to establish baseline function for comparison. Participants that withdraw from any aspect of the study will continue to be cared for per the standard of care.

7.4. Stopping rules (By the Data Safety and Monitoring Committee)

The DSMC shall have authority to stop a research protocol in progress and remove individual human participants from a research protocol. The Data Safety and Monitoring Committee may request enrollment be suspended due to safety concerns.

8. Data analysis and statistical considerations

8.1. Statistical Analysis

The primary endpoint is the clinician-evaluated SFGS. We will compare the pre-post change (at baseline and 4 months) in SFGS between the treatment arms. Statistical analyses will be based on a treatment difference relative to baseline at 4 months in a linear random effects model with: a group difference at baseline, a time (0/1) variable indicating 4 months versus baseline, a group-by-time interaction representing the treatment difference, and a random effect at the subject level.

8.2. Sample size and power calculation

Each arm will contain 18 participants, for a total of 36 participants. In previous work, we observed a change from baseline in SFGS of 9.4 with a standard deviation of 7.1 and intra-subject correlation of pre-post measurements of 0.86. Assuming the same standard deviation, a correlation of 0.5, and a loss of follow up of 10%, with a mean treatment difference of 7 points between arms, the planned sample size will provide approximately 80% power.

Patients will be recruited from the Facial Nerve Clinic at the University of Wisconsin Hospitals and Clinics. This is a high-volume tertiary care center with approximately 6 new synkinesis patients per clinic, making our pool of eligible participants approximately 72 patients per year. With an accrual goal of 36 participants within 1 year, we would need to recruit 50% of eligible patients over the year.

8.3. Analysis of endpoints

To reduce the risk of bias, two Department of Surgery research employees will independently grade videos and photos in a blinded fashion using the Sunnybrook Facial Grading System instrument. Video recordings will be presented in random order to two trained research assistants. Ten percent of samples will be included twice to measure intra-rater reliability. Twenty percent of samples will be re-scored by the other rater to measure inter-rater reliability. Ms. Jackie Diels will be responsible for rater training prior to the investigation, and during the study Dr. Mark Lucarelli will provide independent oversight, ongoing training, and resolution of scoring disagreement. At the conclusion of the study, study biostatistician Dr. Bret Hanlon, who generated the randomization sequence, will perform data analysis comparing mean changes between groups and account for participant drop out if necessary.

Our qualitative analysis will proceed concurrently with data collection to allow identified themes to be explored in subsequent interviews. In qualitative research this involves both coding the written transcripts and then modeling the coded data. All team members will analyze the data and look for themes and trends that are emergent from the data. For the pre-treatment interviews, we will employ Conventional Content Analysis15 which will allow us gain direct information from study participants without imposing preconceived categories or theoretical perspectives. For the post-treatment interviews, we will switch to directed content analysis as the findings from pre-treatment interviews will guide our analysis of post-treatment interviews, while capturing emergent themes that come up in the data. We will establish reliability in our analysis through peer debriefing, triangulation, and expert feedback (through Jackie Diels), and member checks. Coded transcripts, the codebook, and descriptions of codes will be maintained using NVivo 11 software (QSR International). As coding evolves, changes will be documented in an audit trail. We will map our findings onto the PROMIS measures; specifically, Social

Functioning and Social Isolation scales, to determine the domains that are important to patients but are not included in current quantitative measures.

9. Risks and benefits of trial participation

9.1. Potential risks

Risks associated with treatment

The two approaches to be compared are both widely adopted as standard of care for the treatment of synkinesis. Botulinum toxin shots have risks. These risks include, but are not limited to, infection, bleeding, bruising, weakness, pain where the shot was given, eyelid drooping, headache, nausea, flu like symptoms, dry eyes, skin rash/itching, and the chance the shot may not fully help. The FDA has issued a black box warning for the potential spread of the botulinum toxin from the site the shot was given. Very rare, serious side effects include allergic reactions, body weakness, double vision, speech issues, trouble breathing, abnormal heart rhythm, or a heart attack. While these risks are small, they can happen each time a shot is given.

Neuromuscular retraining therapy: patients may experience common side effects such as increased muscle/joint soreness or pain. There is a risk that their condition will not improve or possibly worsen. There is a risk of other problems, despite all safety measures taken. Certain underlying conditions may increase the risk and severity of problems.

Risks associated with psychological stress

Participants will be discussing their experiences and any adverse outcomes they have experienced. This may cause changes in thought processes and emotion. These changes will mostly be transitory; however they may be recurrent, or even permanent.

Risks associated with loss of confidentiality

There is a risk that information recorded about participants will be shared with people who would not normally have access to this information.

Unknown risks

This study may involve risks to the participant which are currently unforeseeable. We will inform participants as soon as possible if we discover any information that may affect the participant's health, welfare, or decision to be in this study.

9.2. Mitigation of potential risks

Mitigation of risks associated with treatment

Subjects who would have opted to solely undergo neuromuscular retraining therapy may be exposed to risks of chemodenervation if they are randomly assigned to that procedure. These risks are described in detail to the patient as part of the informed consent process for treatment. Botox injections will be conducted according to standard clinical procedures. Subjects are not seen between Botox treatments, but they are instructed to call with any concerns, questions, or adverse reactions. Patients who are capable of carrying a fetus will be asked before each injection if they are pregnant.

Mitigation of risks associated with psychological stress

The participant showing signs of psychological stress will be reminded of the voluntary nature of the clinical trial they are participating in, and that they can stop at any time without punishment or loss of care. The Primary Investigator will be made aware of any participants displaying these signs by the research staff, and will refer them to appropriate resources as needed.

We are using the HADS and BIPQ questionnaires only for research, not to diagnose mental health issues. We will not tell patients the results. We will advise patients to contact their physician or other health care provider, such as a mental health professional, if they are experiencing emotional distress.

If imminent harm to self or others is identified from participation in the study, patients' responses and health information may be shared with others (e.g., mandatory reporting to authorities or physicians).

Mitigation of risks associated with loss of confidentiality
All information obtained and associated data files will be confidential and will be kept in a locked file or password protected computer. The risk of breach of confidentiality regarding participation in the study outside of the scope of the research will be handled by carefully controlling access to study data only to personnel on the research team.

Confidentiality will be protected further by: (1) using a participant log form that contains only the minimum necessary protected health information (PHI) concerning participants, and storing this log in a locked area when not in use, (2) not sharing PHI with any outside institution, (3) coding data collection forms with a consecutive participant number that is not derived from any participant personal identifiers, and linking that data collection form to the participant log, and (4) storing the participant log and data collection forms separately.

It is highly likely that these measures will result in avoidance of breach of confidentiality outside of the research. In addition, the data to be collected are not sensitive to participants. A data and safety monitoring board will also be in place.

9.3. Potential benefits and risk-to-benefit ratio

Potential benefits to the individual participant
Individual benefits to participants are not guaranteed, as this study is seeking to determine which of the two accepted standard of care treatments participants could receive will yield the best clinical benefits.

Potential benefit to society
We will gain scientific and clinical understanding of impaired facial mobility caused by synkinesis with regard to social functioning and quality of life, allowing us to understand the devastating effects of synkinesis that require clinical attention. Further, this work will explore the efficacy of neuromuscular retraining therapy for patients with synkinesis, thus closing a critical gap in knowledge concerning efficacious treatments for this condition. Finally, this work leverages the volume of patients seen at the University of Wisconsin Facial Nerve Clinic, and is significant in its prospective randomized design to measure therapy against established chemodenervation effects.

In addition, our unique qualitative data analysis, could potentially lead to the development of a novel way for clinicians and researchers to measure symptoms and outcomes in patient populations. This could lead to more patient-centered care. It could also reduce the need to administer other instruments, which can be time-consuming and may miss important indicators of disease status and well being.

Risk-to-benefit ratio
Although individual benefits to participants are not guaranteed, it is anticipated that considerable societal benefit will result from the proposed studies. Currently both management approaches proposed are accepted standards of care. The reason this study is essential is that currently the evidence cannot support one treatment over another and therefore we feel that this study has true equipoise. The

results of this study can be used to help guide the treatment of synkinesis and help provide solid evidence to support future guidelines.

10. Adverse events and unanticipated problems

10.1. Adverse event definitions

Adverse event (AE)

An adverse event is defined as any untoward or unfavorable medical occurrence in a human participant including any abnormal sign, symptom, or disease temporally associated with the participant's participation in the research, whether or not considered related to the participant's participation in the research. Adverse event collection will begin at Day of Treatment Onset and continue through the last assessments. Untoward medical occurrences or acute conditions that occur between screening and surgery will be recorded as medical history.

Serious adverse event (SAE)

A serious adverse event is defined as any adverse event that meets one of the following criteria:

- Results in death; OR
- Is life-threatening; OR
- Requires hospitalization or prolongs existing hospitalization; OR
- Results in significant or persistent disability or incapacity; OR
- Results in a congenital anomaly/birth defect; OR

Unanticipated problem (UP)

An unanticipated problem is defined as an event that meets all of the following criteria:

(1) unexpected in severity, nature, or frequency given the research procedures and the characteristics of the participant population (i.e., problems that are not described in this protocol or other study documents); AND

(2) related or possible related to participation in the research; AND

(3) suggests that research places participants or others at a greater risk of harm related to the research than was previously known or recognized.

10.2. Severity assessment and Grade

The severity of all adverse events will be assessed according to the following scale:

- Mild = does not interfere with the participant's usual function
- Moderate = interferes to some extent with the participant's usual function
- Severe = interferes significantly with the participant's usual function

The grade is assessed according to the Common Terminology Criteria for Adverse Events (CTCAE), Version 5.0.

- Grade 1: Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; or intervention not indicated.
- Grade 2: Moderate; minimal, local or noninvasive intervention indicated; or limiting age-appropriate instrumental activities of daily living (e.g. preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.)
- Grade 3: Severe or medically significant but not immediately life-threatening; or hospitalization or prolongation of hospitalization indicated; or disabling; or limiting self-care activities of daily living (e.g. bathing, dressing and undressing, feeding self, using the toilet, taking medications, not bedridden, etc.)
- Grade 4: Life-threatening consequences; or urgent intervention indicated.

- Grade 5: Death related to AE.

10.3. Causality assessment

The PI will determine the relationship of adverse events to the research intervention using the following scale:

- Definite = AE is clearly related to the study procedures
- Probable = AE is likely related to the study procedures
- Possible = AE is possibly related to the study procedures
- Unlikely = AE is doubtfully related to the study procedures
- Unrelated = AE is clearly not related to the study procedures

10.4. Procedures for recording and reporting adverse events

Adverse events greater than or equal to CTCAE Grade 3 will be recorded as the study team becomes aware of them. Adverse events will be reported per IRB guidelines.

11. Trial safety monitoring

11.1. Data Safety Monitoring Plan

The type of data or events to be captured under the monitoring plan:
Adverse events greater than or equal to CTCAE Grade 3 will be recorded as the study team becomes aware of them. In addition, any protocol deviations and violations and unanticipated problems will be assessed for this study.

The person responsible for monitoring the data collected:
Principal Investigator
Scott Chaiet, MD, MBA, FACS

The frequency of assessments/analysis of data or events captured by the monitoring plan:
In addition to the study team recording and assessing events in real time, the study monitor will review all events annually. The study team will also have a standing meeting once per month and schedule additional meetings as needed.

Time frame for reporting:
Events will be reported per IRB guidelines.

Stopping rules:
Action will be taken when a pattern occurs of events indicating an increase in the risks of study participation. A change in the risk/benefit ratio will be reported to the IRB.

Procedures/time frame for reporting outcomes of monitoring reviews:
Events meeting reporting requirements will be reported to the IRB per IRB guidelines.

Plans to monitor adherence to the IRB-approved protocol:
Protocol adherence will be reviewed during monthly study team meetings as well as by the study monitor during his annual review.

12. Administrative requirements

12.1. Good clinical practice

The study will be conducted in accordance with FDA and ICH guidelines for Good Clinical Practice. All study staff will be thoroughly familiar with the contents of this protocol and associated trial materials.

12.2. Data quality assurance

The investigator is required to prepare and maintain adequate and accurate case histories designed to record all observations and other data pertinent to the study for each study participant. Study data will be entered into an electronic case report form (eCRF) by site personnel. Any changes made to study data will be made to the CRF.

12.3. Study monitoring

Due to financial and staff limitations there are no formal plans for outside monitoring of data for this study.

12.4. Ethical consideration

The study will be conducted in accordance with ethical principles founded in the Declaration of Helsinki. The IRB will review all appropriate study documentation in order to safeguard the rights, safety and well-being of the participants. The study will only be conducted at sites where IRB approval has been obtained. The protocol, informed consent form, written information given to the patients, safety updates, annual progress reports and any revisions to these documents will be provided to the IRB by the investigator.

12.5. Patient confidentiality

Information about study participants will be kept confidential and managed according to the requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA). Those regulations require a signed subject authorization informing the participant of the following:

- what protected health information (PHI) will be collected from participants in this study
- who will have access to that information and why
- who will use or disclose that information
- the rights of a research participant to revoke their authorization for use of their PHI

All participants will be assigned a study-specific ID number. We will maintain a master list linking each participant's medical record number (MRN) with a study-specific ID number. This list is to be maintained in a location separate from any study data. Only study staff listed on the IRB application shall have access to the list.

All information obtained and associated data files will be confidential and will be kept in a locked file or password protected computer. The risk of breach of confidentiality regarding participation in the study outside of the scope of the research will be handled by carefully controlling access to study data only to personnel on the research team.

Confidentiality will be protected further by: (1) using a participant log form that contains only the minimum necessary protected health information (PHI) concerning participants, and storing this log in a locked area when not in use, (2) not sharing PHI with any outside institution, (3) coding data collection forms with a consecutive participant number that is not derived from any participant personal identifiers, and linking that data collection form to the participant log, and (4) storing the participant log and data collection forms separately.

All study data will be kept for 10 years after publication of study findings. All data will be destroyed by deletion from computer files and/or shredding.

12.6. Investigator compliance

The investigator will conduct the trial in compliance with the protocol approved by the IRB. Changes to the protocol will require written IRB approval prior to implementation, except when the modification is needed to eliminate an immediate hazard(s) to participants.

12.7. Participant cost and payment

Cost

As we expect to align study activities with clinic visits, participants are not expected to incur additional costs. Participants or their insurance company will still be responsible for the cost of treatments. They will also have to pay for basic expenses like childcare, food, or transportation related to visits.

Payment

Participants will be provided $25 in reimbursement for each completed interview.

13. Funding sources

This study is being funded by the UW-Madison Department of Surgery.

14. Publication policy

This study will be registered with ClinicalTrials.gov.

15. Bibliography

1. Baugh, R.F., et al., *Clinical practice guideline: Bell's palsy.* Otolaryngology–Head and Neck Surgery, 2013. **149**(3_suppl): p. S1-S27.
2. Engström, M., et al., *Prednisolone and valaciclovir in Bell's palsy: a randomised, double-blind, placebo-controlled, multicentre trial.* The Lancet Neurology, 2008. **7**(11): p. 993-1000.
3. Mehta, R.P., M. WernickRobinson, and T.A. Hadlock, *Validation of the synkinesis assessment questionnaire.* The Laryngoscope, 2007. **117**(5): p. 923-926.
4. Nakamura, K., et al., *Biofeedback rehabilitation for prevention of synkinesis after facial palsy.* Otolaryngology—Head and Neck Surgery, 2003. **128**(4): p. 539-543.
5. Lindsay, R.W., M. Robinson, and T.A. Hadlock, *Comprehensive facial rehabilitation improves function in people with facial paralysis: a 5-year experience at the Massachusetts Eye and Ear Infirmary.* Physical therapy, 2010. **90**(3): p. 391-397.
6. Akulov, M.A., et al., *IncobotulinumtoxinA treatment of facial nerve palsy after neurosurgery.* Journal of the neurological sciences, 2017. **381**: p. 130-134.