Comprehensive Cardiac Rehabilitation Feasibility After Stroke – CCR FAST

IRB: A18-361
NCT: 03944668

Clinical Study Protocol

Amendment 2 Date: 25 September 2020

Sponsor
Regions Hospital Medical Staff
Research, Education and Development (RED) Fund

This study will be conducted in compliance with the protocol, IND regulations and other applicable regulatory requirements.

PROTOCOL SIGNATURE PAGE

I have read this protocol and agree to adhere to the requirements. I will provide copies of this protocol and pertinent information to the study personnel under my supervision and my hospital ethics committee/institutional review board (EC/IRB). I will discuss this material with them and ensure they are fully informed regarding the study medication and the conduct of the study according to this protocol, applicable law, applicable regulatory requirements, general standards of good clinical practice and hospital EC/IRB requirements.

_____

Principal Investigator

_____

Date

PROTOCOL AMENDMENT, VERSION 1
RATIONALE

CCR FAST Protocol has been amended to account for the COVID-19 pandemic, which has resulted in increased health and safety concerns for study participants, their caregivers, and clinical site staff because of the risks of person-to-person transmission of disease.

Because of anticipated disruptions in follow-up visits associated with the global COVID-19 pandemic, the 6 month visit has been amended. Recently care delivery has initiated in-person visits within HealthPartners and Cardiac Rehabilitation in-person appointments have resumed. The final 8 study subjects will be completing the 6 month study visit in May/June timeline will have the following*:*

Specific data points in the protocol, along with a rationale for each change, are summarized below:

- Complete Cardiac Rehabilitation Visits ***–in-person visits conducted in align with care delivery*.**
- 6 Month Final Visit ***– conduct by phone or video visit.***
- Quality of Life, Mood and Cognitive Functioning Questionnaires ***-Questionnaires that can be obtained by phone or video visit.***
- Blood Test ***–Obtain historical results from medical records so not to require an additional in-person visit.***
- 24 Hour Ambulatory Blood Pressure –***Not obtained so not to require additional in-person visits. During all Cardiac Rehabilitation visits blood pressure, heart rate are being monitor.***
- Brain MRI (Magnetic Resonance Imaging) – ***To be obtained at Neuroscience Center Imaging Department --this is the Primary Endpoint for the study.***

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PROTOCOL SYNOPSIS

PROTOCOL TITLE	Comprehensive Cardiac Rehabilitation Feasibility After Stroke
SHORT TITLE	CCR FAST
STUDY PHASE	Enrollment Complete
STUDY OBJECTIVES AND PURPOSE	
Study Purpose The purpose of this study is to demonstrate the feasibility and safety of including stroke patients in a comprehensive cardiac rehabilitation (CCR) program, while examining the clinical value in reducing stroke recurrence, myocardial infarction, readmission, and mortality in stroke patients.	
Primary Objective • To assess the feasibility of comprehensive cardiac rehabilitation for stroke patients.	
Secondary Objective (s) • To explore the potential benefits of cardiac rehabilitation for stroke patients by describing the 6-month rates of recurrent stroke, myocardial infarction, hospital readmission for a cardiovascular or cerebrovascular indication, silent stroke on MRI and death.	
STUDY DESIGN	
Study Type	Feasibility
Study Indication Type	Intervention
Study Design	This study is a prospective feasibility study, which will consist of a single arm of ischemic stroke patients. Seventeen patients will be consented through rolling recruitment to participate in a 36-session CCR program over 12-week period at Regions Hospital Outpatient Cardiac Rehabilitation facility. Participants will join the existing cardiac rehabilitation program, and undergo the same types of exercise therapy and education as the cardiac patients, with slight modifications to the educational material to include brain pathology. The primary endpoint of the study is the successful completion of the study protocol, which consists of attending 75% of the CCR sessions, completing brain MRI and laboratory tests at the end of the study, and attending the end of study visit. Baseline data will be collected while patients are admitted at Regions Hospital. If patients need more time to recover, baseline visits will take place at HealthPartners Neuroscience Center within 3 months from the time of stroke. CCR sessions will also begin within 3 months after the patient's admission for ischemic stroke. The research staff will conduct a 6-week phone call (6-weeks after beginning CCR) to determine if any adverse events (AE) or serious adverse events (SAE) have occurred and to obtain and updated medication list. The 3-month and 6-month clinic visits will take place at the Neuroscience Center and will be 3 months and 6 months from the date of the baseline visit. Patients will meet with Dr. Haitham Hussein and the research staff. The patients' vitals will be

	taken and standard assessments (described below) will be performed, which are typically performed as standard of care. The 6-month clinic visit will also include laboratory tests and a MRI. 24-hour ambulatory blood pressure will be monitored and recorded at baseline and at 6-months. The chart below includes the visit schedule and data collection information.	
Planned Duration of Subject Participation	The duration of study participation for each subject is anticipated to be 6 months from baseline.	
OUTCOMES	Primary-Completion rate	• CCR sessions • 6-month study visit, MRI and labs
	Secondary-Benefit	• 6-month rates of recurrent stroke, myocardial infarction, hospital readmission for a cardiovascular or cerebrovascular indication, silent stroke on MRI and death. • Beginning and end comparison of weight, BMI, blood pressure, and laboratory values
SUBJECT SELECTION		
Targeted Accrual	For this study, we will enroll 17 eligible ischemic stroke patients. We will continue to recruit patients until the 17th patient is enrolled in CCR.	

Inclusion Criteria

- Age ≥ 18 years
- Patient has suffered an ischemic stroke
- Patient should be ambulatory (non-disabling stroke) to be able to participate in the CCR exercise program
- Patient is able to start cardiac rehabilitation within 3 months of stroke

Exclusion Criteria

- No baseline (index admission for ischemic stroke) MRI completed
- Life expectancy < 1-year
- Presence of brain hemorrhage: intracerebral hemorrhage, subarachnoid hemorrhage, subdural hematoma, or epidural hematoma
- Concurrent diagnosis of seizure disorder
- Patient with moderate or severe neurologic deficits, limiting their ability to participate in the CCR exercise program
- Cardiopulmonary conditions preventing the patient from participation, such as severe heart failure, severe aortic stenosis, and exercise-induced asthma
- Patient with cognitive dysfunction impairing their ability to follow directions
- Anticipated procedures such as carotid stenting, carotid endarterectomy, and intracranial aneurysm coiling
- Patient unable to commit to the frequent visits of the CCR program
- Participation in other interventional research (observational research is allowed)
- Unable to have brain MRI
- Non-English speaker
- Pregnant women

1. INTRODUCTION

There is a significant overlap in risk factors (e.g. hyperlipidemia, hypertension, smoking, diabetes, obesity, and a sedentary lifestyle) between ischemic stroke and coronary artery disease.[1-4] These risk factors contribute to the development and progression of atherosclerosis, which is a major cause of ischemic stroke and coronary artery disease. This is why prevention strategies for coronary artery disease and stroke are similar.

Comprehensive cardiac rehabilitation (CCR) is standard-of-care after myocardial infarction, which includes aerobic exercise, education/counseling, and medication compliance oversight. CCR has been shown to improve vascular risk factor control and survival rates, as well as reduce re-infarction and hospital readmission rates.[5-10] CCR has become an integral part of care for many cardiac and pulmonary diseases and is reimbursable by insurance companies. As for stroke, only a few studies have examined the use of CCR and these studies focused on assessing the impact of the program on risk factors control such as cholesterol level, blood pressure, and exercise endurance. No studies examined the impact of CCR on clinical endpoint in stroke patients, such as stroke recurrence, readmission, occurrence of other vascular events, and death. Due to this lack of evidence, CCR is not reimbursable for a stroke diagnosis.

The standard of care after stroke, revolves around restoring the functions lost by stroke through engaging in physical, occupational, and speech therapies. This is a fundamental philosophical difference between CCR and stroke rehabilitation. The former aims to improve wellness and bring the patient to a healthier state compared to baseline, while the latter aims to bring the patient back to baseline. Another important difference between CCR and stroke rehabilitation is the extent and intensity of patient education; while there is an education curriculum for CCR, stroke patients' education typically involves a discussion with providers during hospitalization or clinic visits counsel regarding risk factors. Coaching provided by the CCR program (e.g. helping patients implement a healthier lifestyle and ensuring medication compliance) is lacking in post-stroke care.

A few studies have attempted to integrate CCR after stroke. These studies showed that CCR has short-term beneficial effect on vascular risk factors control (blood pressure, lipid profile, body mass index) and exercise endurance.[11,12] However, none of these studies specifically evaluated the effect that CCR has on clinical endpoints such as stroke recurrence and hospital readmission.

The overall goal of this study is to assess the feasibility of stroke patient participation in Regions Hospital's CCR program. Our study will examine the ability of stroke patient to complete the current CCR program (provided as standard of care by cardiology department). The program consists of 3 sessions per week over 12 weeks. Exploratory endpoints will be the event rate of recurrent stroke at 6 months, MI, death, hospital readmission for a cardiovascular or cerebrovascular indication, and silent stroke on MRI. These analyses will help us with our future power analysis for a subsequent larger trial. The experience, workflow, and the knowledge gained from this study will be used to design a larger study, comparing CCR with conventional post-stroke treatment.

2. SUMMARY OF INTERVENTION DESCRIPTION

For the study intervention, all patients will be prescribed 36 sessions of comprehensive cardiac rehabilitation, which will occur over 12 weeks. Participants will attend the standard of care ongoing cardiac rehabilitation sessions at Regions Hospital Outpatient Cardiac Rehabilitation facility at 2575 University Ave. in St. Paul, MN. The cardiac rehabilitation program is staffed by exercise physiologists, registered dieticians, and registered nurses, under the direction of a cardiologist. The cardiac rehabilitation program includes supervised exercise, nutritional counseling, medication review, and patient education. Stroke patients will receive the same education sessions as the cardiac patients, except for three sessions. Because there were three sessions that were specific to cardiac patients (and therefore not relevant to stroke patients), these sessions will be replaced with three stroke specific education sessions, which were developed by Dr. Haitham Hussein.

Each session will last approximately 60-90 minutes, and include 30-40 minutes of aerobic exercise, 15 minutes of strength training, and a 30 minutes group education session. Patients will be instructed to exercise at a rate of perceived exertion of 11-13 on the Borg scale, corresponding to "fairly light" to "somewhat hard".[13] Exercise intensity will be increased 0.5-1 metabolic equivalent every 1-3 weeks according to patient exercise training parameters. There are 16 educational modules that will be presented to the patients at the group education sessions. The educational material will be modified to include brain pathology.

At the initial CCR visit, an ambulatory blood pressure monitor will be placed on and sent home with the patient. The patient will be monitored for 24 hours and asked to return to the outpatient cardiac rehabilitation facility the next day to return the monitor.

If a patient drops out of the study or stops attending CCR classes, the research staff will call the patient to ask why he or she stopped attending CCR. If the research staff is unable to reach the patient after two phone call attempts, they will attempt to reach the patient at his or her next Neuroscience Center clinic visit to obtain a drop out reason. In addition, adverse or serious adverse events will be monitored by the study staff throughout the study.

3. OBJECTIVES

3.1. Primary Objectives

To assess the feasibility of comprehensive cardiac rehabilitation for stroke patients.

3.2. Secondary Objectives

To explore the potential benefits of cardiac rehabilitation for stroke patients by describing the 6-month rates of recurrent stroke, myocardial infraction, hospital readmission for cardiovascular or cerebrovascular indication, silent stroke on MRI and death.

4. STUDY DESIGN

This study is a prospective feasibility study, which will consist of a single arm of ischemic stroke patients. Seventeen patients will be consented through rolling recruitment to participate in a 36-session CCR program over 12-week period at Regions Hospital Outpatient Cardiac Rehabilitation facility. Participants will join the existing cardiac rehabilitation program, and undergo the same types of exercise therapy and education as the cardiac patients, with slight modifications to the educational material to include brain pathology. The primary endpoint of the study is the successful completion of the study protocol, which consists of attending 75% of the CCR sessions, completing brain MRI and laboratory tests at the end of the study, and attending the end of study visit.

Baseline data will be collected while patients are admitted at Regions Hospital. If patients need more time to recover, baseline visits will take place at HealthPartners Neuroscience Center within 3 months from the time of stroke. CCR sessions will also begin within 3 months after the patient's admission for ischemic stroke. The research staff will conduct a 6-week phone call (6-weeks after beginning CCR) to determine if any adverse events (AE) or serious adverse events (SAE) have occurred and to obtain and updated medication list. The 3-month and 6-month clinic visits will take place at the Neuroscience Center and will be 3 months and 6 months from the date of the baseline visit. Patients will meet with Dr. Haitham Hussein and the research staff. The patients' vitals will be taken and standard assessments (described below) will be performed, which are typically performed as standard of care. The 6-month clinic visit will also include laboratory tests and a MRI. 24-hour ambulatory blood pressure will be monitored and recorded at baseline and at 6-months. The chart below includes the visit schedule and data collection information.

5. PATIENT SELECTION

5.1. Inclusion Criteria

All ischemic stroke patients admitted to Regions Hospital within the study period will be identified.

- Age ≥ 18 years
- Patient has suffered an ischemic stroke
- Patient should be ambulatory (non-disabling stroke) to be able to participate in the CCR exercise program
- Patient is able to start cardiac rehabilitation within 3 months of stroke

5.2. Exclusion Criteria

A subject will not be included for consideration in this study if any of the following criteria are met:

- No baseline (index admission for ischemic stroke) MRI completed
- Life expectancy < 1-year

- Presence of brain hemorrhage: intracerebral hemorrhage, subarachnoid hemorrhage, subdural hematoma, or epidural hematoma
- Concurrent diagnosis of seizure disorder
- Patient with moderate or severe neurologic deficits, limiting their ability to participate in the CCR exercise program
- Cardiopulmonary conditions preventing the patient from participation, such as severe heart failure, severe aortic stenosis, and exercise-induced asthma
- Patient with cognitive dysfunction impairing their ability to follow directions
- Anticipated procedures such as carotid stenting, carotid endarterectomy, and intracranial aneurysm coiling
- Patient unable to commit to the frequent visits of the CCR program
- Participation in other interventional research (observational research is allowed)
- Unable to have brain MRI
- Non-English speaker
- Pregnant women

6. STUDY ASSESSMENTS AND PROCEDURES

6.1. Study Assessments

6.1.1. National Institutes of Health Stroke Scale (NIHSS)

NIHSS is a tool used to evaluate stroke severity.[14,15] The total score ranges from 0-42, with a higher stroke indicating a more severe stroke.

6.1.2. Modified Rankin Scale (MRS)

MRS is a tool used to evaluate the level of disability after stroke.[16] The assessment ranges from 0-6, where 0 is no symptoms at all and 6 is dead.

6.1.3. European Quality of Life Scale (EQ-5D)

The EQ-5D is a tool used to measure health-related quality of life.[17] The tool includes the following dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. The scale ranges from 5-25, with 5 indicating no problems and 25 indicating extreme problems.

6.1.4. Patient Health Questionnaire (PHQ-9)

The PhQ-9 is a tool used to assess depression severity.[18] The scale ranges from 1-27, with a score of 1-4 indicating minimal depression and a score of 20-27 indicating severe depression.

6.1.5. Montreal Cognitive Assessment (MoCA)

The MoCA is a brief cognitive screening tool for detecting cognitive impairment or dementia.[19] The assessment measures multiple cognitive domains including attention, concentration, executive function, memory, language, visuoconstructional skills, conceptual thinking, calculations, and orientation. The scale ranges from 0-30, with a lower score indicating worse cognitive function.

Because the MoCA is assessed three times within 6-7 months, we plan to use different versions to reduce the possibility of a learning effect. Occupational therapy completes a MoCA assessment during inpatient stroke admission and utilizes version 7.1, so the MoCA score will be extracted from the patient's chart. For the 3-month clinic assessment we will use version 7.2 and for the 6-month clinic assessment we will use version 7.3. These are standardized approved versions.

6.2. Procedures

6.2.1. Visit 1: Screening/Baseline (Regions Hospital or HealthPartners Neuroscience Center)

- Obtain written informed consent from subject (or subject's legally authorized representative) prior to any study related procedures.
- Review Inclusion/Exclusion criteria.
- Review medical history, as it pertains to inclusion/exclusion criteria, such as research diagnosis, disease severity, and course of stroke.
- Obtain demographic information.
- Obtain details of medications.
- Collect vital signs; heart rate, blood pressure, oxygen saturation, height, and weight.
- Obtain NIHSS score.
- Obtain MRS score.
- Administer MoCA if not previously measured.
- Administer PHQ-9.
- Retrospectively collect medical information on laboratory tests, vascular imaging, MRI, and echocardiogram.

6.2.2. Visit 2: 6-Week Phone Call (From start of cardiac rehabilitation)

- Gather information on cardiac rehabilitation progress.
- Review current medications.
- Record AEs/SAEs.
- 3-month clinic visit will be scheduled 3-months since start of cardiac rehabilitation.

6.2.3. Visit 3: 3-Month Clinic Visit

- Collect vital signs.
- Review current medications.

- Administer MoCA.
- Complete EQ-5D.
- Complete PHQ-9.
- Obtain NIHSS score with physician.
- Obtain MRS score with physician.
- Record AEs/SAEs.
- 6-month MRI and clinic visit will be scheduled 6-months since start of cardiac rehabilitation.

6.2.4. Visit 4: 6-Month MRI and Clinic Visit

- Undergo MRI.
- Collect laboratory samples; lipid panel, basic metabolic panel, coagulation panel, glycosylated hemoglobin, and Cotinine.
- Collect vital signs.
- Review current medications.
- Administer MoCA.
- Complete EQ-5D.
- Complete PHQ-9.
- Obtain NIHSS score with physician.
- Obtain MRS score with physician.
- Record AEs/SAEs.

*This visit may be separated into 2 visits, if needed.

6.3. Early Withdrawal

If a patient drops out of the study or stops attending CCR classes, the research staff will call the patient to ask why he or she stopped attending CCR. If the research staff is unable to reach the patient after two phone call attempts, they will attempt to reach the patient at his or her next Neuroscience Center clinic visit to obtain a drop out reason. In addition, adverse or serious adverse events will be monitored by the study staff throughout the study.

6.4. Safety

For all safety assessments described below, any clinically significant change will be recorded as an AE or SAE.

6.5. Vital Signs

Vital signs and O_2 saturation will be recorded at visits 1, 3, and 4 and recorded prior to the MRI and blood draw. For within subject consistency, brachial artery pressure will be obtained in the routine fashion and the same arm will be used for all study measurements.

Blood pressure and heart rate will be measured after subject has been sitting quietly for a minimum of 5 minutes. Vitals signs and O_2 saturation will be monitored by clinical staff during each visit of the study.

6.6. Weight

Body weight will be measured at visits 1, 3, and 4, without heavy outer clothing or footwear.

6.7. MRI

A standard MRI will be performed on all subjects at visit 4. This will be performed prior to the clinic visit.

6.8. Laboratory Samples

During visit 4, participant will undergo a blood draw. The following laboratory tests will be performed: lipid panel, basic metabolic panel, coagulation panel, and glycosylated hemoglobin. Any abnormal laboratory results at this visit will be communicated by the Principal Investigator or study staff to the physician and the patient. This can be obtained before or after MRI and clinic evaluations.

7. SUBJECT COMPLETION AND WITHDRAWAL

7.1. Subject Completion

Subjects completing all 3 study visits and 75% attendance of CCR sessions will be considered to have completed study.

7.2. Subject Withdrawal

Subjects may withdraw from study at any time for any reason without penalty or be terminated from the study by the clinical investigator (see provisions for termination by study team.) The investigational team will document the reason(s) for withdrawal. In the event a subject chooses to withdraw from study before Visit 4, the safety procedures described in Section 6.2.4. will be collected within 14 days following subject's decision to withdraw. For all subjects who withdraw, all final safety assessments will be collected regardless of time elapsed since the previous visit. In addition to final visit, subjects who withdraw early will be contacted within 7 days by study staff via telephone to assess for the development of any new and/or ongoing AEs and concomitant medications. Efforts will be made to recruit subjects to replace any withdrawals so as to maintain an n=17.

Subject's participation may be terminated at the discretion of the investigator. Individuals may be withdrawn for the following reasons:

- Clinically significant adverse events
- Lost to follow-up
- Protocol violations
- Inability to tolerate study intervention
- Other

8. ADVERSE EVENTS (AE) AND SERIOUS ADVERSE EVENTS (SAE)

8.1. Definition of AE

An adverse event is any symptom, sign, illness or experience which develops or worsens in severity during the course of the study. Interval development of illnesses or injuries will be regarded as adverse events. Abnormal results of diagnostic procedures are considered to be adverse events if the abnormality:

- Results in study withdrawal
- Is associated with clinical signs or symptoms
- Leads to treatment or to further diagnostic tests
- Is considered by the investigator to be of clinical significance

8.2. Definition of SAE

Adverse events are classified as either serious or non-serious. A serious adverse event is any event that results in:

- Death
- Life-threatening situation
- Hospitalization or prolongation of hospitalization
- Disability or incapacitation
- Other events determined by investigator to be medically significant in which subject's well-being is jeopardized (e.g. events that have high likelihood of escalating to the point of meeting criteria outlined above)

8.2.1. Clinical Laboratory Abnormalities and Other Abnormal Assessments as AEs and SAEs

Any new abnormal, vital, examination, or laboratory finding judged clinically significant by the investigator will be documented as an AE or SAE, if meeting the definitions for such. Abnormal lab findings or other abnormal assessments associated with the disease under study will not be considered AEs or SAEs unless more severe than expected, as judged by the investigator.

8.2.2. Time Period and Frequency of Detecting AEs and SAEs

Upon consenting, a subject is considered to be a participant in the study, and until that person either withdraws or completes study, AEs and SAEs will be recorded. The investigational team will promptly report any AE/SAE as required per federal guidelines.

9. DATA ANALYSIS AND STATISTICAL CONSIDERATIONS

9.1. Statistical Analysis

The statistical analysis plan was written by Lauren O. Erickson, Biostatistician at the HealthPartners Institute. She will also perform the statistical analyses for the study.

9.2. Preliminary Analysis

Descriptive statistics, such as mean and standard deviation (for continuous variables) and frequency (for categorical and binary variables) will be computed for all demographic variables. Population demographics will include age, gender, stroke type, labs, BMI, and others.

No imputation for missing data or adjustment for multiple comparisons will be done as they were deemed too conservative for this feasibility study. All statistical analyses will be performed in SAS 9.4 with $p<0.05$ considered to be statistically significant.

9.3. Primary Analysis

The primary goal of this feasibility study will be to determine the study completion rate. This will be defined as 75% attendance at CCR sessions, acquisition of 6-month MRI and labs, and attendance of end of study visit. We will calculate and report the 95% confidence interval for this rate. We will also report the number of charts reviewed, the number of patients screened for inclusion/exclusion criteria, the number of patients contacted for the study, the number of patients that agreed to participate, the number of patients that started CCR, and the number of patients that dropped out or completed CCR. We will also describe reasons for non-completion.

9.4. Secondary Analyses

For the secondary analyses, we will explore the potential benefits of cardiac rehabilitation for stroke patients by describing the 6-month rates of recurrent stroke, myocardial infarction, hospital readmission for a cardiovascular or cerebrovascular indication, silent stroke on MRI and death. We will assess the individual and composite event rates by calculating the mean and 95% confidence interval. This will provide information to allow us to power a larger study.

Additionally, we plan to descriptively compare weight, BMI, blood pressure, and laboratory values at the beginning and end of the study. We will do this by calculating the mean and 95% confidence intervals for these values.

9.5. Study Power

Our sample size is based on the capacity of the CCR course as deemed by the cardiac rehabilitation program. With a sample size of 17, we will be able to estimate a completion rate of 75% to within a 95% confidence interval of ± 20.2%.

10. STUDY CONDUCT CONSIDERATIONS

10.1. Regulatory and Ethical Considerations

The study will be conducted in accordance with GCP guidelines. Subject privacy requirements will be observed, as well as the fundamental concepts of the Declaration of Helsinki (e.g. IRB approval of the study, obtaining informed consent from all subjects and meeting all reporting requirements).

10.2. Quality Assurance

In the event of a regulatory agency audit or inspection, the site will allow the auditor/inspector access to all records documented and facilities utilized in conducting the study. The site will also make accommodations (e.g. time, schedule) to discuss findings, concerns, and questions with auditor/inspector.

10.3. Study Closure

Upon completion of all subject visits, data entry and analysis, the investigator will inform the local IRB of study closure.

10.4. Records Retention

All site records will be maintained and stored in a safe and secure location for a minimum of 15 years post study completion.

10.5. Provision of Study Results and Information to Investigators

The study results will be made available by the study statistician once the analysis is complete.

10.6. Data Management

Data collection and reporting tools will be developed and stored internally (e.g. Case Report Forms and source documents [Paper/REDCap]). Data collected and stored electronically will remain confidential and secure (e.g. secured server and password protected files [REDCap]). Study binders will be stored in a locked file cabinet within a locked office. After the study is closed, all subject identifiers will be destroyed.

11. REFERENCES

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