Dual Antiplatelet Therapy Adherence With Reminder App Usage

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Study Protocol

A. Study Title and Investigators

Dual Antiplatelet Therapy Adherence With Reminder App Usage

Principal Investigator	*David Altschul, MD* *Department of Neurosurgery* *3316 Rochambeau Ave, Bronx, NY 10467-2841* *Phone #: 718-820-3243* *Email: daltschu@montefiore.org*
Co-Investigator	Samuel Ahmad
Research Staff	Erida Castro-Rivas, Wenzhu Mowrey, PhD
Title	Dual Antiplatelet Therapy Adherence With Reminder App Usage
Study Design /Methodology	Randomized Control Trial
Study Duration	6 months
Objectives	To examine the level of compliance with DAPT of patients assigned to a medication reminder app compared to that of patients not using the app receiving the same standard of care.
Number of Subjects	68
Eligibility Criteria and main objective	See pertinent sections below
Study Site	Single Center
Study Funded	No

INVESTIGATOR'S QUALIFICATIONS AND EXPERIENCE

□ A copy of C.V./resume for each attending/faculty investigator, HIPAA and Human subjects protection training for all research team members are included with this protocol, if not in IRB files. (Please ensure that all research personnel included above have completed training in the protection of human subjects as per iRIS requirements.)

CONFLICTS OF INTEREST STATEMENT

□ A statement of financial disclosure and other conflicts of interest of all investigators and research personnel is included in the iRIS initial review application form for chart reviews.

(Please verify if any members of the research team have any conflict of interest related to this study. Please ascertain this prior to submission- contact iRIS for guidance)

B. Research Proposal:

1. Introduction

Medication compliance adherence is of the utmost importance in medicine and has significant impact on clinical outcomes. New technologies, such as smart phones, are currently utilized for a plethora of purposes. By developing an app-based medication reminder system for patients undergoing procedural treatment of aneurysms, the study authors hope to significantly enhance medication adherence as well as clinical outcomes. This study compares dual antiplatelet therapy [DAPT] adherence of the patients using this app and the patients receiving only the standard of care. Questions from the Adherence Barriers Questionnaire [ABQ] will be utilized to assess adherence and relevant clinical outcomes will be used as well.

2. Background

Flow-diverter devices (FDDs) such as the Pipeline Embolization Device (PED) are next-generation stents that are placed at neck of the aneurysm in order to significantly diminish blood flow into the aneurysm, which ultimately results in aneurysm thrombosis. Another method used to treat aneurysms is stent-assisted coiling. These procedures, however, bring with them risk of stroke and thrombosis/stenosis and thus require antiplatelet medications both prior to and post treatment.

Dual antiplatelet therapy [DAPT] in the form of aspirin and clopidogrel, a thienopyridine, is most common. A survey by Faught *et al.* found that among neurointerventionalists practicing in America, the most commonly prescribed antiplatelet therapy was aspirin 325 mg and clopidogrel 75 mg daily for seven days or five days prior to the procedure. Maintenance therapy following FDD placement is commonplace, with only 15.6% and 30.2% of practitioners refraining following intracranial and cervical stent placement, respectively. Aspirin 325 mg daily for life and clopidogrel 75 mg daily for three months was the most common maintenance therapy aside from the choice “other” [2].

Discontinuation of antiplatelet medication has been found to be associated with thrombotic events. A review article by Briganti *et al.* reported a mean incidence of 3.8% for parent artery thrombosis or 50 percent or greater stenosis during the FDD

implantation procedure in 12 studies. An occlusion or stenosis rate of 6.8% by the time of angiographic follow-up was found in 16 studies. Mean angiographic follow-up was nine months, with a range of three to thirty months. The authors note that these later findings were frequently incidental and were associated with termination of clopidogrel [1]. This association has also been found in the case of stent-assisted coiling. Mocco *et al.* found that seven out of 213 patients who received stent-assisted coiling of aneurysms developed delayed thrombotic events. Furthermore, the authors reported that prior to these events, the patients were not taking DAPT, which consisted of aspirin and clopidogrel [6].

Thromboelastography [TEG] is commonly used to assess the clotting ability of blood. In neuroendovascular procedures such as PED implantation, TEG evaluates the effectiveness of antiplatelet therapy. The hepatic CYP450 system is responsible for converting clopidogrel and prasugrel, two thienopyridines, into their active forms [4]. As reported by Norgard *et al.*, whereas clopidogrel metabolism is reduced in patient's carrying a reduced-function CYP2C19 allele, prasugrel metabolism does not appear to be affected to any clinically significant degree. Cosequently hyporesponders to clopidogrel are at elevated risk of thrombosis [8]. McTaggart *et al.* found that among the eight patients out of 31 who had suffered thromboembolic events/TIA following PED placement, six were hyporesponders to clopidogrel on TEG [5].

Noncompliance with DAPT may have clinically significant consequences. The CDC states that several factors influence medication compliance. These factors include the severity of the health condition and the patient's beliefs about his or her condition, busy schedules that make it difficult to remember to take medicines, out-of-pocket cost of medications, and possessing an understanding of when to take medications [10]. Prasugrel, for example, can be prohibitively expensive for some patients due to higher out-of-pocket costs. Fortunately, smart phone app-generated reminders to take medications may enhance compliance by providing patients with clear instructions wherever they happen to be.

Text-based reminders have been shown to decrease medication noncompliance. Park *et al.* explored the impact of text messaging on antiplatelet and statin adherence among patients who had suffered an MI or received percutaneous coronary intervention [PCI]. The mean age was 59.2 years. Text medication reminders required acknowledgement of receipt. Patients who received text messages took a significantly greater percentage of correct doses taken [p= 0.02] and percentage of prescribed doses taken [p=0.01] compared to those who did not receive such reminders. No significant difference in percentages of doses of statins taken was found [9]. Foreman *et al.* found that patients who received text message reminders regarding chronic oral medications were significantly more likely to take the appropriate dosages. Regarding antidiabetes medications, the text message cohort had a mean compliance rate of 0.91 compared to a rate of 0.82 for the control group (p=0.029). A significant increase in β-blocker compliance was also found,

with a mean compliance rate of 0.88 for the text message cohort opposed to a 0.71 rate for the control group (p=0.006) [3].

The advent of an antiplatelet reminder app for FDDs and stent-assisted coiling holds the possibility of not only improving medication compliance but also of decreasing the incidence of thrombotic events following said procedures. The effectiveness of this app may be assessed via a prospective cohort study. We would like to develop a tailored standardized intervention for endovascular patients receiving DAPT that extends beyond the traditional teach-back method and follow-up evaluation.

3. Research Question:

To test the efficacy of a medication reminder app regarding DAPT compliance, with compliance estimated by patients' ABQ scores. The free app is called Endovascular Neurosurgery and is available on the Apple App Store. It was developed by Dr. Jonathan Nakhla and does not collect user data. The only data inputted into the app are the patient's procedure date and the antiplatelet medications the patient has been prescribed. The app does not possess patient data. Montefiore IT stated that it does not monitor apps that patients download onto their own devices. Both groups will receive the same standard of care, including any information on the risks of DAPT nonadherence.

C. Research Population or Study Sample Selection

1. Study Setting:

The target population will be adult aneurysm patients from Montefiore's cerebrovascular neurosurgery clinic. All consultations and introductions to the study will take place in the 3316 Rochambeau Ave, and participants will be selected based on their willingness to participate in the study and possession of an iphone.

2. Source of subject selection:

A qualified research staff member will approach potential participants. They will be recruited in the waiting room area by face-to-face meetings. A screening questionnaire (APPENDIX 1-Attached Eligibility Form) will be utilized to identify subjects for inclusion in the study.

3. Sampling Strategies:

We plan to enroll 68 patients undergoing either FDD placement or stent-assisted coiling at baseline. Upon consent, the patients will be randomized with 1:1 ratio into one of the 2 arms: the intervention arm (standard of care + medication compliance app) and the comparison arm (standard of care).

3.1 Randomization: Participants will be randomized at the cerebrovascular neurosurgery clinic prior to the start of the intervention. Randomization will be performed using a random number generator.

Equitable Selection of Subjects

i) **Gender of Subjects:** No exclusion by gender. Women and men are included in this research.

ii) **Age of Subjects:** By the nature of the study all subjects to be included in the study are adults ≥ 18 years of age.

4. Potential Issues/Problems with Specific Sub-Groups

No specific issues related to study procedures are expected given the minimal risk nature of these procedures. However, language barriers to understanding the questionnaires will be overcome by utilizing appropriate translations of questionnaires, study material and through study personnel who are bilingual.

D. Study Criteria

1. Inclusion Criteria:

i) Over 18 years old
ii) Must speak either English or Spanish fluently
iii) Physically able to come to the research site location.
iv) Elective stent-based procedures for unruptured cervical, and intracranial, intradural aneurysms
v) Endovascular therapy must be deemed appropriate by clinical team.

2. Exclusion Criteria

i) Presence of basilar, cavernous, or ruptured aneurysms. Presence of comorbidities that preclude the possibility of treatment. Presence of contraindications to DAPT. Presence of certain vessel anatomical characteristics. Lack of iphone.

E. Methods and Procedures

1. Materials and Methods

i. Objectives:

To examine the level of DAPT adherence between patients who receive medication reminder notifications vs those who only receive the standard of care.

ii. Study Design:

This will be a randomized control trial, with patients undergoing stent-based endovascular treatment for unruptured cervical and intradural, intracranial aneurysms. Informed consent will be obtained from participating patients and the study will be conducted after being approved by local ethics committees. Patients will be assigned to either the app group or the control group.

The particular stent-based therapy, either FDD placement or stent-assisted coiling, will be chosen for each patient by the clinical team. During the study consultation, the app group will have the app installed on their smart phones and will be trained in its usage. TEG and Aspirin inhibition percentage will be determined for each patient following the procedure. Patients with TEG less than 60% will have DAPT changed from 81 mg aspirin and 75 mg clopidogrel to 81 mg aspirin and 10 mg prasugrel. Patients with aspirin inhibition percentages of less than 20% will have their aspirin doses increased to 325 mg. Medication compliance of all participants will be assessed on the day of the procedure via a medication compliance questionnaire. The same questionnaire will be administered during follow-up appointments 2-4 weeks and 6 months post-procedure.

2. **Study Procedures**

i. Recruitment and Enrollment

Participants will be recruited in Montefiore's cerebrovascular neurosurgery clinic. The initial recruitment plan is that research staff will use standardized scripts to describe the study and its purpose highlighting eligibility criteria, including both gender and English and/or Spanish speaking. Interested individuals will be asked to indicate their interest in the study to the research staff who will invite them to complete the informed consent process and an eligibility questionnaire. Both the app and questionnaire will be available in Spanish. As part of the consent process, patients will be shown and taught how to use the app.

ii. Intake Process

Study staff will conduct all intake processes (i.e., informed consent and screening) at the site. In instances where participants are not comfortable proceeding with the study, they will be withdrawn by research staff. Staff will meet in an alternative private setting in the clinic.

3. **Data Collection and Management**

Patient data will be stored on a document accessible only with a password. We will use codes for each patient and said codes will be stored in a separate database to match with the names of the patients. We will not publish any identifying patient data.

i. Survey Data Management

All local staff will be trained in maintaining participant confidentiality and rigorous data management based on standard operating procedures. All electronic files will be reviewed for completeness and accuracy.

ii. Qualitative Data Management

All interview guides will be translated to Spanish and confirmed by a second qualified translator to ensure accuracy prior to conducting the interviews.

iii. Data Storage and Confidentiality:

The principal investigator and research team will be responsible for ensuring the physical privacy of participants and that data are stored in a secure area accessible only to study staff. All efforts will be made to protect subject personal information. Medical information of research study subjects will be stored and kept in a designated research office according to requirements and they will not be identified personally in any reports or publications resulting from this study.

iv. Screening: The screening time will start at the time of the consultation. After patients agree that they will be part of the study, eligibility verification will take place. Randomization will take place and patients will be assigned to either the app or control group. We plan to enroll 68 patients undergoing either FDD placement or stent-assisted coiling at baseline. Upon consent, the patients will be randomized with 1:1 ratio into one of the 2 arms: the intervention arm (standard of care + medication compliance app) and the comparison arm (standard of care). Block randomization with the block size of 10 will be used to generate the randomization scheme using the SAS procedure called proc plan.

Patients in the app group will have the app installed on their devices and will be trained in using the app. Demographic data will also be harvested from all patients.

Once the app is installed, patients may input their procedure type and date. Patients then will select the antiplatelet medications that have been prescribed and schedule a time to receive medication reminders. The medication(s) and time of usage will be selected following the shared-decision making process between the attending physician and patient. These medication reminders may be turned off at any time on the app. Upon receiving a medication reminder, the patient must only unlock his or her phone to end the reminder message.

v. Procedure: Approximately 1 week post-screening patients will undergo their procedures. The ABQ will be administered to all patients.

vi. Follow-up plan:

1. 2-4 weeks post-procedure: This will serve as standard follow-up for all patients. The ABQ will be administered to all patients for a second time.

2. 6 months post-procedure: Standard follow-up will occur for all patients. The ABQ will be administered a third and final time.

3. Outcomes related to morbidity and mortality will be collected for all patients at 2 to 4 weeks and 6 months post-procedure.

4. Closure or termination of study: Once data collection and analysis are complete, the study will be closed.
5. **Sample Size**

We plan to enroll 68 patients undergoing stent-based aneurysm procedures (25 in the app group and 25 in the control group) at baseline.

vii. Data Safety and Monitoring: Given that the intervention is non-harmful [an app], we do not believe that a Data Safety Monitoring Plan will be necessary. The trial will go to completion.

F. Analysis

i. Statistical plan:

All analyses will be performed according to intention to treat, where patients are analyzed as randomized. Baseline characteristics will be compared between arms using Pearson's Chi-square or Fisher's exact test for categorical variables and using 2-sample t-test or Wilcoxon rank sum test for continuous variables. The primary end point is ABQ medication compliance score. Within-arm analysis: Paired t-tests will compare ABQ scores between pre-procedure and 6 months within each arm. Primary analysis will use the 2-sample t-test to compare the ABQ score at 6 months between the two arms. These analyses will be repeated for the pre-procedure and the intermediate time point (2-4 weeks) to assess whether ABQ scores are improved with a shorter intervention period. Linear regression models will compare ABQ scores at 6 months between the 2 arms while adjusting for potential confounders such as age, sex, race/ethnicity, potential out-of-pocket expenses, and cigarette smoking status. Linear mixed models accounting for repeated measures from the same patient will be used to compare the effects of the arms (App vs. usual care) and time points while adjusting for potential confounders.

ii. Power analysis:

The study sample sizes of 25 in the App arm and 25 in the usual care arm will achieve 80% power to detect a minimum group difference of 0.80 SD between the two arms in the ABQ scores at 6 months for medication compliance with a significance level (alpha) of 0.05 using a 2-sided 2-sample t-test.

iii. Outcome measures:

Primary endpoint: medication compliance score from the Adherence Barrier Questionnaire [ABQ]. The ABQ score ranges from 14-52 and a higher score indicates that a patient faces greater barriers to adherence [7].

Assessment time points: App usage will commence when medication use is initiated 7 days prior to the procedure. The ABQ will be given 3 times: on the day of the procedure, 2-4 weeks post-procedure and 6 months post-procedure. 6-month is the primary time point.

Safety endpoints: incidence of stroke/thrombotic events/TIAs at 6 months post-treatment, as well as all-cause mortality, all-cause morbidity, rehospitalization for cerebrovascular events, peri-treatment hospitalization lasting more than 15 days, and delayed discharge from hospital.

G. Risk/Benefit Assessment

i. Risk

One possible risk is that participants may feel uncomfortable in sharing their health information with investigators and or research staff regarding their healthcare and demographic information. However, participation in this study is strictly voluntary and participants may leave the study at any point or refuse to answer any question. Participants also have the option to report to the project administrators any event during the study that causes any discomfort. It is important that participants know that they will not be penalized nor will their care or benefits at Montefiore be at risk if participants choose to share withhold this information.

ii. Protection against Risks

All necessary precautions will be taken to ensure that the information collected during the study is safe-guarded. Additionally, as part of the process involved in obtaining written informed consent, all participants will be reminded that their responses are confidential and that they may refuse to participate in the project or withdraw at any time without explanation, and further, that such action will in no way affect their

employment, treatment or future interactions with their supervisors or health care providers. To ensure confidentiality, all patient data will be stored in a repository accessible only with a password. We will use codes for each patient and said codes will be stored in a separate database to match with the names of the patients. We will not publish any identifying patient data.

iii. Potential Benefits to the Subjects.
We cannot and do not guarantee that participants will receive any benefits from this study. The benefit for the community at large is that the collected data will be used to establish a standard medication adherence intervention, tailor-made for cerebrovascular neurosurgery patients.

iv. Alternate procedures.
Instead of being in this study, participants have these options: They do not have to participate in this study to receive ongoing care for their current conditions. Additionally this is not a study that will diagnose or treat a disease or condition in subjects. Participants are free to choose not to participate in the study.

H. Subject Identification, Recruitment and Consent

i. Process of Consent
All eligible participants will be required to review and sign an informed consent form in their preferred language before participating in the pilot test. The research coordinator will be present to explain the consent form in its entirety. This research coordinator will answer any questions or concerns raised by any participant during the consent form review and the consent process will be documented by the research coordinator. All participants will receive a copy of their signed consent form after assuring that they have understood what was said and can repeat to the proctor specific security/rights procedures. (IE: the participant knows that he or she does not risk the care they receive at Montefiore by not committing to the study.) The PI is responsible for ensuring that valid consent is obtained and documented for all subjects.
These consent forms will be created utilizing the IRB templates at iRIS Center in both English and Spanish and will be approved by the IRB.
ii. Subject Capacity
All the potential participants will be asked if they have decisional capacity.
iii. Subject/Representative Comprehension
The study staff (PI or research coordinator) will explain the consenting process in detail including all required elements of the consent process in participant's language. A read back of the essential items of the consent will be conducted by the staff to ensure adequate understanding by the participant of the consent and study procedures, risk, benefits and alternatives.
All assessment materials will be created in both English and Spanish by qualified individuals to safeguard each participant's autonomy. Materials will first be created in

English and upon IRB approval be translated into Spanish by qualified personnel. These new materials will then be subjected to IRB amendment approval before formal use. All translation of project materials will be performed by qualified individuals and certified in writing as per IRB requirement. All procedures will be executed according to participant disposition and be further divided and executed based on each participant's most convenient language; in either Spanish or English. None of the materials will be formally administered until review boards from the participating site - Einstein IRB - approve their use and language.

iv. Consent Forms

Written informed consent will be obtained and will be made available in English and Spanish. (See APPENDIX #2: (Informed Consent Document)

v. Documentation of Consent

The study staff will review the consent form, explain the critical components and obtain written documentation through signatures from each participant prior to enrollment into the study.

vi. Costs to the Subject

There will be no cost for participation.

vii. Payment for Participation

There will be no payment for participation.

I– Conflicts of Interest

There is no conflict of interest for any authors in this study.

J– Reporting Results

All results will be analyzed and manuscripts will be prepared for submission to an academic medical journal for publication. We are also aiming to present these findings in regional or national conferences.

Work Cited

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