MASH Study (**M**emory training in **A**neurysmal **S**ubarachnoid **H**emorrhage Patients)

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Study Title: MASH Study (**M**emory training in **A**neurysmal **S**ubarachnoid **H**emorrhage Patients)

Hypothesis: Periodic online cognitive exercises improve memory function in cognitively disabled aneurysmal subarachnoid hemorrhage patients

Background and Rationale:

Ruptured cerebral aneurysms affect nearly 40,000 individuals annually in the United States and unlike other causes for stroke, have not decreased in incidence. Its burden is of concern given that the peak age of rupture is 52. As such, aneurysmal subarachnoid hemorrhage (SAH) is responsible for a disproportionately high burden of long-term disability among all stroke patients. Furthermore, population-based survival rates have improved for these patients. Therefore, among this growing number of survivors, are a growing number with no physical limitations yet burdened by substantial cognitive deficits that variably impair their quality of life. Their outward physical appearance and neurologic examination can be deceiving with regards to their functional status.

Cognitive deficits are a common challenge in patients with ruptured cerebral aneurysms. At three months of follow up, nearly 95% of patients report at least one cognitive or emotional complaint that hampers everyday functioning[2]. The most frequently cited complaint involves memory, attention and mental slowness(2). Specifically, this involves strategic and organizational processes, referred to as executive function(4). Sheldon et al studied 24 SAH patients with matched controls and found SAH patients had greater difficulty with unorganized lists of items to remember as opposed to organized lists. They postulated that this deficit was due to a disconnection between different cognitive processes that were needed to work together for demanding tasks, which was in essence, executive functioning(5). Another described memory deficit specific to SAH was cognitive inflexibility, whereby there is difficulty shifting attention between tasks. Executive functioning allows planning, suppression of automatic actions and monitoring behavior to adjust attention for different tasks (6). Without this ability, one is unable to move from one task to another and then return. They become unable to move fluidly between tasks and often report that when forced to change tasks, they are unable to return to what they were previously doing.

Anecdotally, in our practice, which specializes in the care of brain aneurysm patients, these concerns surface again and again. It is precisely because of this pattern we observed while caring for patients with previously ruptured brain aneurysms that prompted us to look for solutions to address this seemingly unmet clinical need.

These deficits are particularly insidious because they may be overlooked by the physician or family. Nevertheless, when asked, patients report cognitive deficits to be one of their most disabling deficits (7)Oftentimes, these deficits can only be detected with neuropsychological testing, which may not be accessible or available to many patients.

Often patients who report these problems have a favorable recovery in the hospital and are discharged home and are largely able to care for themselves. The primary deficit keeping them from functioning as they did prior to the ruptured aneurysm is a lasting memory deficit.

Prior approaches to this issue include goal management training and cognitive therapy. Goal management training has been proven to be effective in executive function rehabilitation following brain injury in adults (8). GMT is a rehabilitation technique aimed at helping patients with executive impairments to better structure (instrumental) activities of daily living ((i)ADL). GMT entails learning and applying an algorithm, in which complex tasks are subdivided into multiple task steps. Both, the final goal and the task steps leading to this goal have to be kept active in working memory due in part that GMT is focused on making one aware of the cognitive weakness one has to allow for a behavioral change to modify the outcome. Unfortunately, working memory processes are often impaired in patients with executive deficits. GMT focuses on changing the particular strategy for completing a task rather than targeting the specific deficit (8). Monitoring goal-directed behavior and the correct execution of task steps are the main aims of GMT, which requires sustained attention to allow for change (8).

Another option is cognitive therapy, which focuses on one particular area of interest such as working memory, reasoning or processing speed. A small study in Sweden was able to show that cognitive therapy provided benefits in working memory, attention and overall reduced the subjective cognitive complaints after 5 weeks of intervention for patients after stroke (9,10).

What may be more helpful to these patients is a resource that is more convenient, less costly, and yet effective in alleviating the types of memory difficulties oftentimes seen after SAH. Online-based cognitive interventions may represent one such option. Online cognitive interventions are becoming increasingly available and offer easier access, easier delivery, and the ability to track and analyze performance on these exercises in an automated fashion. Administering exercises using paper and face-to-face encounters requires significant time and effort to deliver. *Lumosity*, one such program, claims to bolster cognitive performance by regular engagement in various games and mental exercises. It has been studied in patients with cancer related and traumatic brain injury patients. Significant improvements in processing speeds, mental flexibility and memory have been reported. No similar interventions have been reported in patients within the first few months after an aneurysmal SAH. Given the unique characteristics of many patients who survive a ruptured brain aneurysm, and the feasibility of using online cognitive interventions, we sought to evaluate its effect through a clinical randomized control study.

Study Plan:

Our study aims to determine if periodic online cognitive exercises improve memory function in ruptured cerebral aneurysm patients with disabling baseline memory deficits within the first 12 months. Eligible subjects will be physically independent but have a self-reported disabling memory deficit within the first year of their ruptured cerebral aneurysm. Screening will be determined by a series of questions either in person or over the telephone. All enrolled subjects will complete memory assessments to determine baseline function.

Assessments:

Redcap administered assessments:

1. CLCE-24

This questionnaire was originally designed to be a diagnostic instrument for clinicians treating patients after a subarachnoid hemorrhage. This questionnaire addresses the most common cognitive and emotional complaints for patients who have experienced a subarachnoid hemorrhage highlighting the number of unresolved sequelae from a subarachnoid hemorrhage. The average number of complaints in this survey is 3.3 with 2.3 from cognitive and 1 from emotion problems. This study does not have a normal value but rather it was found that those that score higher were found to correlate with significantly lower CAMCOG (a standardized instrument for the diagnosis and grading of dementia) and MMSE (Mini-mental status exam) scores compared to those without complaints. This questionnaire shows no significant differences in scoring regardless for age, gender or education.

2. Working memory

This questionnaire was developed to assess the different areas of working memory including attention, executive function and working memory allowing patients to self-report their problems, which is beneficial for this patient population due to the awareness of their memory deficits. This questionnaire was developed for patients who had TBI, ischemic or hemorrhagic strokes. This survey allows us to not only assess what aspect of working memory is affected but also allows us to grade the severity. The test divides each question in to the sub-section it is testing and allots 40 points per section or 120 total. The average score of healthy individuals is 17.8 (SD:11.5) whereas, those with brain injury 34.5 (SD: 22.1)

3. Activity of Daily Living

To determine the extent by which these problems affect daily life for the individual, we are including the Activity of Daily Living (ADL) questionnaire. This survey assesses standard areas of daily living to determine the number as well as the severity of the problem. This survey was designed such that patients with cognitive decline could still yield meaningful responses. This test determined normative values based on comparing a patient's baseline status to their overall score on the survey, which allows it to be sensitive to mild decline as well as severe decline in cognitive function. The test is scored by taking the total score of a patient and dividing by the number of items rated which allows the test to only measure deficits seen with activities that the patient regularly participates in. This test has a validated cut off points for determine positive results: 0-33% may indicate some impairment, 34-66% moderate impairment, 67+%: severe impairment.

Lumosity administered assessments:

1. Arithmetic Reasoning
2. Forward Memory Span
3. Reverse Memory Span
4. Digit Symbol Coding
5. Divided Visual Attention
6. Trail Making A
7. Trail Making B
8. Progressive Matrices

Then, randomization will occur to a treatment group, which will include online access to structure-oriented activities(Lumosity), and an active control group(online crosswords).

Intervention group: Participants assigned to the intervention/experimental group will undergo twenty training sessions over 10 weeks. In each session, they practice video games selected from *Lumosity*(http://www.lumosity.com), a web-based cognitive training platform that includes games designed with the purpose of improving the user's cognitive abilities (Stemberg et al., 2013). Games will be customized using an automated algorithm supplied by Lumosity, to determine performance in the various targeted skills, which include: task switching, logical reasoning, quantitative reasoning, response inhibition, numerical calculation, working memory, face-name recall, selective attention, spatial recall, spatial orientations, planning, and divided attention.

Game Name	Targeted Skill
Brain Shift	Task Switching
Brain Shift Overdrive	Task Switching
By the Rules	Logical Reasoning
Chalkboard Challenge	Quantitative Reasoning
Color Match	Response Inhibition
Disconnection	Task Switching
Disillusion	Task Switching
Division Storm	Numerical Calculation
Ebb and Flow	Task Switching
Face Memory Workout	Working Memory
Familiar Faces	Face-Name Recall
Follow that Frog	Working Memory
Lost in Migration	Selective Attention
Memory Lane	Working Memory
Memory Match	Working Memory
Memory Match Overdrive	Working Memory
Memory Matrix	Spatial Recall
Moneycomb	Spatial Recall
Monster Garden	Working Memory
Pet Detective	Planning
Pinball Recall	Working Memory
Playing Koi	Divided Attention
Raindrops	Numerical Calculation
Rhyme Workout	Working Memory

River Ranger	Information Processing
Rotation Matrix	Working Memory
Route to Sprout	Planning
Star Search	Selective Attention
Tidal Treasures	Working Memory
Train of Thought	Divided Attention
Trouble Brewing	Divided Attention
Word Sort	Logical Reasoning

Lumosity has the ability to customize games based on the performance in five different cognitive domains. Based on the participants' performance on exercises testing speed, memory, attention, flexibility and problem solving, certain online games can be emphasized based on the needs of the patient. Of interest will also be the profile of cognitive deficits determined by the Lumosity screening process that may characterize the cognitive problems typically seen in patients with ruptured cerebral aneurysms. Based on prior literature, we will be focusing on games designed to improve divided attention, flexibility, problem solving and memory

The recommended interaction would be 2 hours per week for 10 weeks for a total training time of 20 hours over the course of the study.

Active control group: The attention control group uses a computerized crossword puzzle game. This game offers a choice between three puzzle sizes, three levels of complexity, and varying font sizes. It also includes optional help features such as filling in an unknown letter or word. There is, however, no progressive challenge to the user by either increased speed, visual field size, number of distractors, or degree of difficulty of target stimulus differentiation. Thus, the crossword puzzle program provides an appropriate, computerized attention control alternative to the active visual speed of processing training.

To facilitate rapid recruitment into the study, randomization stratification will not be performed. After 10 weeks, both groups will complete the assessments that were used at enrollment.

Research Methods and Procedures for Post SAH Memory Study

Recruitment and Screening:

Recruitment: Study participants will be recruited in the following ways:

A. *Neurosurgery Clinic Setting:*

a. Patients with ruptured aneurysms that will be coming in for follow up at Rush's Neurosurgery Clinic Office can be recruited for the study. If a patient is deemed a good candidate for the study by Dr. Michael Chen or Megan Konopka, they will discuss the study with the patient at the end of their clinic visit. If the patient is willing to participate, they may be consented. After agreeing, patients will be sent an email with a secured link via REDCap to fill out a demographics survey.

B. *Email and Phone Screen Setting:*

a. Dr. Chen has composed a recruitment letter to patients that can be emailed. With that letter, patients will receive contact information of who to call if interested in the study. The contact will be the Neurosurgery Department's research coordinator Michelle Smreczak. It will be the coordinator's responsibility to screen these potential participants over the phone. At

this point, if the patient qualifies and agrees to the study, a telephone script of the consent will be read to the patients. After agreeing, patients will be sent an email with a secured link via REDCap to fill out a demographics survey.

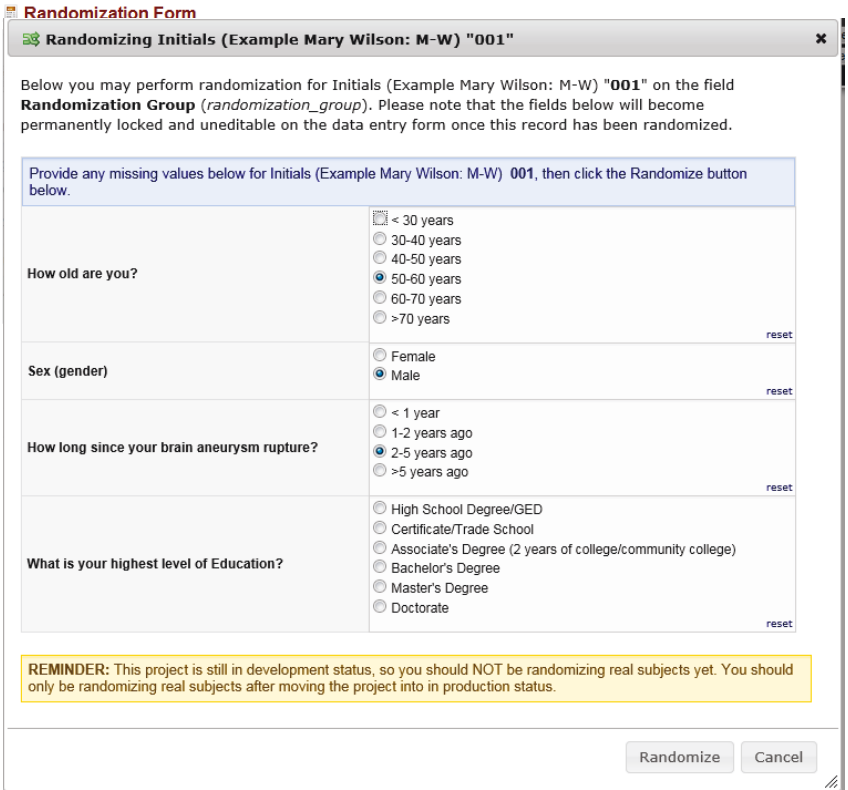
C. Social Media
    a. Via the Brain Aneurysm Foundation or the Joe Niekro Foundation
        i. Survivors who meet the inclusion criteria via a telephone interview, will be enrolled in the study.

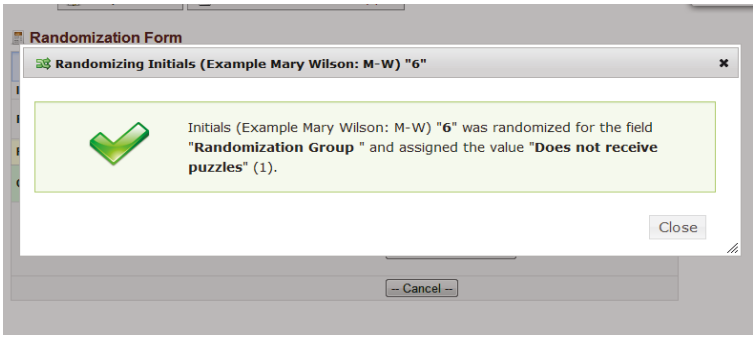
D. Support Group Setting at Rush University Medical Center:
    a. Patients with ruptured aneurysms that attend a Rush initiated monthly support group will be recruited for this study. Recruitment scripts will be provided to the facilitator of the group. If patients are interested in participating, they will be able to speak with Investigator Megan Konopka and sign a consent form after the monthly meeting. Both the facilitator and Investigators will make it very clear in their scripts that participation in the study is voluntary and not necessary to do as part of the support group meetings.

Data Collection Methods:

A. REDCap is a secure web application that is used for building and managing online surveys and databases. The REDCap Consortium is composed of 1,308 active institutional partners in 88 countries who utilize and support the system. REDCap will be used for the following in this proposed study:
    a. Participant Randomization
        1. Study staff will be utilizing REDCap's randomization tool. The randomization tool has been formatted to randomize patients into one of two groups, "Lumosity" or "active control". **Stratification factors will include age (<50, 50 or older), gender, level of education (greater than high school education or not) and time since rupture of the aneurysm (<6 months or 6-12 months)**. Randomization by the study staff will occur when the participant completes the demographic survey. This tool will help the study better implement a defined randomization model and allow the study staff to randomize participants easily.

Screen shots of the Project's Randomization Tool:

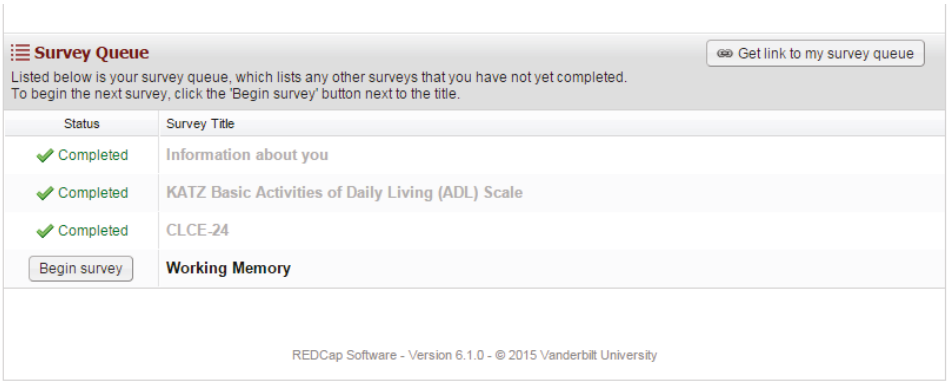




b. Delivery of patient surveys

1. Surveys (CLCE-24, Working Memory, and Activities of Daily Living ADL Scale) will be sent to participants via the REDCap system. Study participants will be able to complete all surveys and submit them online. Individual emails are sent out to each person in the study. The email will contain brief instructions about completing the survey and a secured link to their individual survey queue.

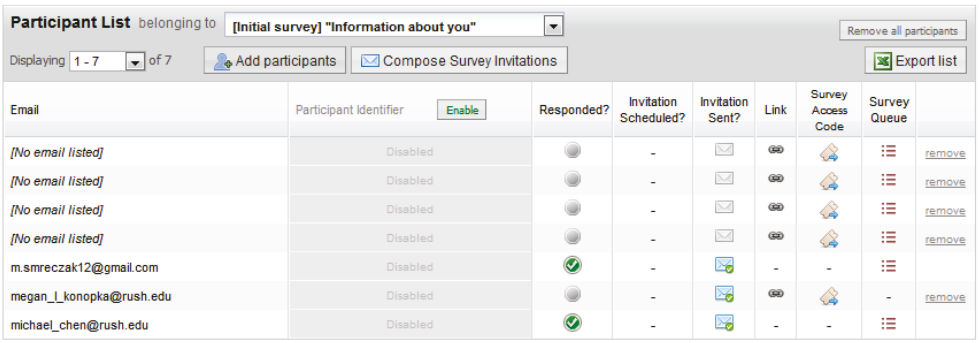
Screen shot of the Survey Queue:



c. Collection of Survey Responses:

1. The REDCap database will alert the study team on which surveys were and were not completed by specific participants. The study staff will be able to send reminders to those who have not yet completed all the required surveys in their queue.

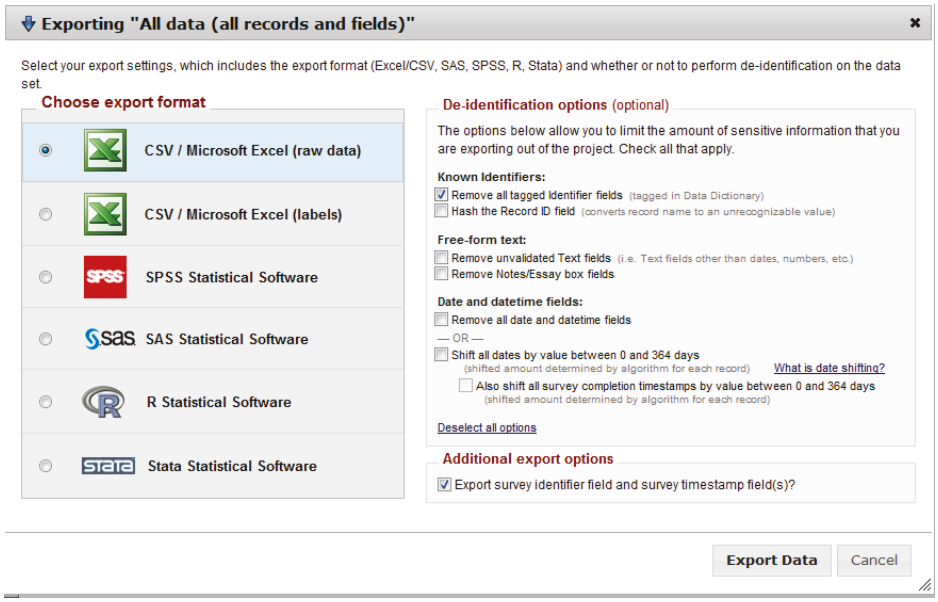
Screen shot of the participant list:



d. Data Export

1. When survey information is collected, the study team will be able to analyze the data that has populated into REDCap in many different ways. The Data can be exported into many different programs such as SPSS or excel.

Screen shot of data export options:



Screening Process:

Objective: To best validate that the subject, particularly those who are not actual patients, have the index disease being studied.

Screening Questions:

1. What were your symptoms that led to the diagnosis of a brain aneurysm?
2. Did anybody actually tell you that you had bleeding in your head?
3. How long did you stay in the hospital?
4. What did they say caused the bleeding in the brain?
5. How was the aneurysm treated?
6. Are you able to dress yourself, clean yourself and feed yourself?

7. Have you had problems with remembering things, such as appointments, responsibilities that have affected your daily life/activities?
8. Do you feel like you have a problem with memory since your aneurysm rupture?

Inclusion/Exclusion Criteria:

Inclusion
Ruptured cerebral aneurysm-confirmed by study personnel within past year
Age 18 and older
Those with a modified Rankin 0 or 1
Baseline memory problem affecting daily life
Home computer or tablet with internet access

Exclusion
Unable to read or speak English

Data Analysis:
Data will be analyzed by a Spearman rank-order correlation. Data will be compared by using the number of completed puzzles and the amount of time spent completing them with changes noted on the CLCE-24 and working memory questionnaires. The Spearman rank-order will be used to show a monotonic relationship with completing strategy orientated puzzle and reduction in memory symptoms.

Table of Expected Results

Testing	Baseline	Post Intervention	Controls
CLCE-24	Cognitive and Emotional complaints: 3.3	Cognitive and emotional complaints: 1	Cognitive and emotional complaints: 3
ADLQ	Total: 17/84 or 20%	Total: 10/84 or 11%	Total: 18/84 or 21%
Working Memory	Total: 34.5 Storage: 11 Attention: 14 Executive Function: 9	Total: 20 Storage: 6 Attention: 8 Executive Function: 6	Total: 32 Storage: 10 Attention: 14 Executive Function: 8

Estimated sample size: 108 subjects total.
For CLCE-24, a sample size of 50 patients per group (total of 100 patients) can provide 80% power to detect a difference of 2 in number of complaints between the two groups, with a significance level of 0.5 and using a two-sample t-test (two-sided). For the Working memory questionnaire, a sample size of 54 patients per group (total of 108 patients) will achieve 80% power to detect a difference of 12 points between the two groups, with a significance level of 0.5 and using a two-sample t-test (two-sided).

Data Collection:
Data will be collected at different time points in this study. Please refer to table 1 for further reference.

Week 1: Consent, enrollment, completion of three Redcap assessments and Lumosity assessments. Randomization. Intervention group will receive access to Lumosity and control will get access to crossword puzzles.
Weeks 2-9: Intervention group will be reminded to complete Lumosity games; active controls will be reminded to complete cross-word puzzles
Week 10: All subjects complete the three Redcap assessments, the Lumosity assessments. Study completed at this time.

Table 1.

Group	Week 1	Weeks 2-9	Week 10
Intervention			
CLCE24/Working memory/ADLs/Lumosity	X		x
Lumosity	x	x	X
Control			
CLCE24/Working memory/ADLs/Lumosity	X		X
Active control		x	X

*At 70 day assessment, patients will have a +/-10 day window to submit questionnaires.

Data Analysis: The primary analysis should be comparisons between the two groups for the outcome measures. T test or Mann-Whitney test can be used for comparisons and regression analysis may be performed with adjustment of baseline characteristics.

Questionnaires

For the CLCE-24, Working Memory and Activities of Daily Living Questionnaire, please see Appendix A.

Processes and controls to ensure study integrity

A key differentiator in this study is the use of online consent, data acquisition and data analysis. A concern for data being collected in this fashion concerns sampling bias and construct validity. One might think that support groups and online social networks may not capture data from patients who are older and not as familiar with technology. However, as social media improves its user interface, greater numbers of older users are being engaged. We believe *Lumosity* represents one such solution to address this concern. With regard to construct validity, we have included a series of questions we will administer over the phone in the event subjects are not actual patients of our practice for whom we have been able to review the relevant history, physical examination and imaging findings. Users of targeted social network groups are likely to be a self-selected motivated group of individuals. The likelihood that individuals without a diagnosis of brain aneurysm would be a part of this targeted social network and participate in the study seems unlikely. We hope that the relatively larger size of the dataset relative to previously published single-center series can overcome the effect any erroneous outliers may have on biasing the data.

Suitability of investigator(s) and institution

Michael Chen, MD is a board-certified, Associate Professor at Rush University Medical Center. He has over 10 years of experience caring for patients with vascular disease of the brain and spine. As such, annual office visits from patients with cerebral aneurysms average between 150-200. He has been interviewed on ABC, FOX and CBS news as well as the Chicago Tribune and the Wall Street Journal. He's been awarded research grants, authored over 50 peer-reviewed scientific papers, invited to speak at national and international meetings, and is an associate editor for the Journal of Neuro-interventional Surgery. He serves on the Scientific Advisory Boards for the Niekro Foundationand the Bee Foundation. He was elected to the Rush University Medical Staff Executive Committee. He serves on the Standards & Guidelines Committee for the Society for Neurointerventional Surgery.

Dr. Chen has engaged national brain aneurysm support groups to conduct online questionnaires evaluating hypothesis-driven questions on quality of life issues among patients with ruptured brain aneurysms. In 2014, he published an article, “Patient-reported

outcome measures for patients with cerebral aneurysms acquired via social media: data from a large nationwide sample" in the Journal of Neurointerventional Surgery whereby data from over 600 subjects over a 2 month span across 47 states in the United States was obtained Valuable networks and experience were gained from this experience to conduct future clinical studies leveraging social media.

Rush University Medical Center and the Department of Neurological Surgery is a tertiary care, academic urban 800-bed medical center in Chicago, Illinois. We perform the largest number of neurosurgical cases in the city and have been invited to participate in multiple studies evaluating new devices and technologies. We have a monthly support group in our Neurosurgery office for brain aneurysm survivors in conjunction with the Joe Niekro Foundation.

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