PROSPER PROTOCOL

PROSPER (Patient-centered Research into Outcomes Stroke patients Prefer and Effectiveness Research) is a three year research project to create a national, sustainable model to improve decision-making and patient-centered stroke outcomes through comparative effectiveness research.

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Introduction

Stroke is the fourth leading cause of death and the most common cause of long-term disability in the United States. Every 40 seconds, someone in the US has a stroke, with almost 1/4 of these being recurrent strokes. The burden of stroke is disproportionately borne by older patients, women and blacks. The prognosis after stroke remains poor, with 1-year mortality rate of 15-30%. Stroke is the second most common reason for hospitalization among those 65 years or older and the leading cause of long-term disability. After stroke, there are large variations in care, and patients have significant uncertainties regarding the balance of benefits and risks of medications prescribed. To date, clinical trials have enrolled highly selected patients that are not representative of the broader stroke community. This leaves many questions unanswered for real-world stroke survivors on what therapies will have the greatest impact on their well-being.

Most research for stroke is aimed at practitioner-centered treatment in acute care settings. Limited evidence is available to guide stroke survivors to make informed decisions balancing the benefits and risks for improving stroke recovery and prevention of recurrent stroke or complications based on individual preferences, needs, and values. Many stroke survivors express concerns about long-term medication safety and effectiveness, especially given the different characteristics among patients. Many wonder which medications improve (or worsen) time at home, quality of life, activities of daily living, functional status, fatigue, depression or anxiety. Other questions include which medication should be taken among many choices, for how long and the trade-offs regarding long-term health versus potential adverse effects.

Objectives

The overall goal of PROSPER is to create a national, sustainable model to improve decision-making and patient-centered stroke outcomes through comparative effectiveness research. The American Heart Association (AHA), American Stroke Association (ASA), its volunteers, and the Duke Clinical Research Institute (DCRI) propose to address existing evidence gaps and develop the requested data on the range of clinical outcomes that may be experienced by stroke survivors. To achieve these goals, we will link the nation's largest stroke registry, the AHA Get With The Guidelines-Stroke program and nationwide Medicare claims data, coupled with telephone interviews for longitudinal treatment and downstream patient-reported outcomes. We will then conduct series of comparative effectiveness and safety studies that will inform existing and emerging stroke treatment options in order to improve outcomes most important to stroke patients.

Patient-centered Research into Outcomes Stroke patients Prefer and Effectiveness Research (PROSPER) is organized under three specific aims:

Aim 1: To develop a national platform to identify outcomes most desired and prioritized by patients as well as evaluate treatment options.

Aim 2: To apply this platform to conduct comparative effectiveness studies on outcomes as prioritized by patients and other stakeholders in the following treatment areas:

a) Oral Anticoagulation
b) Statin therapy
c) Anti-depressant therapy

Aim 3: To design, evaluate and implement novel decision aids from our comparative effectiveness studies that empower stroke survivors to more effectively make treatment decisions.
The resulting new evidence-based knowledge will help guide individual informed decisions based on patients' unique characteristics and be disseminated widely through 1900 GWTG-Stroke hospitals.

Design and Procedures

Using GWTG-Stroke and associated 1900 hospitals, we will conduct several comparative research protocols prioritized by stroke survivor focus groups and surveys. The PROSPER study is broadly divided into two components: ***retrospective and prospective***. The retrospective component will utilize GWTG-Stroke registry clinical data linked with Medicare claims to assess the effectiveness and safety of post-stroke therapies on long-term clinical outcomes (n= 450,000). The prospective component of PROSPER will use the AVAIL registry (n=3000) combined with additional telephone interviews of 2000 stroke survivors at 3 and 6 months after discharge for a combined cohort of over 5000 patients to obtain detailed information on patient-reported outcomes.

Study Outcomes

The following are candidate outcomes of interest in PROSPER for all three therapeutic areas: We will continually work with patient stakeholders throughout the study to select the outcomes most important to patients.

Retrospective (GWTG-Stroke/CMS Data):

- "Home-time" (days alive and at home)
- Death
- Stroke/TIA readmission
- All-cause readmission
- Cardiovascular readmission
- Bleeding readmission

Prospective (AVAIL/PROSPER):

- Post-stroke fatigue
- Depression
- Medication taking behaviors
- Rankin Scale
- EuroQOL (EQ5D)
- Stroke Impact Scale

Site Selection

Retrospective:
The retrospective portion of the study will perform secondary analysis of data previously collected as part of GWTG-Stroke; therefore, no site recruitment will be conducted.

Prospective:

Hospitals that are already participating in the GWTG–Stroke program will be invited to participate in the prospective component of PROSPER. An AHA collaborator will send a letter to GWTG stroke sites inviting them to participate. All attempts will be made to include a cross-section of hospitals in all regions of the U.S, including certified primary and non-primary stroke centers. Depending on site availability, a balanced design

may be possible (primary stroke centers and non-primary stroke centers). Successful patient enrollment during the AVAIL study will be considered when inviting sites to participate. A webinar/teleconference will be provided by clinical leadership to further explain the goals of PROSPER and answer any questions. Sites that choose to participate will be given recruitment materials and be provided support by the DCRI Operations Team during the recruitment period.

Site/Investigator Obligations

Retrospective:

This portion of the study will perform secondary analysis of data previously collected; therefore there are no obligations for site investigators.

Prospective:

Prior to beginning enrollment, all site investigators and study coordinators will be required to complete necessary legal and regulatory documents, as well as to obtain institutional review board (IRB) approval. Interested hospitals will be provided with a study protocol, an informed consent template, a contract amendment template, and associated study documents. This project protocol and the informed consent document must be approved by an IRB at each site.

The site will not be activated to enroll until the DCRI Coordinating Center has received written documentation of IRB authorization for this study, a copy of the approved informed consent form and an executed site contract. Study investigators must comply with yearly IRB reviews of this protocol and must provide the DCRI with corresponding written IRB renewal acknowledgments.

Subject Selection

Retrospective:

This portion of the study will perform secondary analysis of data previously collected; therefore we will neither recruit nor consent subjects. There is no direct patient contact for this portion of the study. These data are part of the GWTG-Stroke Registry; analyses of these data are covered under an existing IRB approval # Pro00002534. The GWTG-Stroke data will be supplemented with CMS (Centers for Medicare and Medicaid Services) claims data. This linked dataset is covered under the same IRB (DUA # is 17758). We will only use ischemic stroke registry patient data.

Prospective:

DCRI will educate sites on the following patient-level inclusion/exclusion criteria:

Inclusion Criteria: Consistent with GWTG inclusion criteria, patients must be ≥18 and have a primary diagnosis of acute ischemic stroke.

Additional inclusion criteria specific to this study are as follows:

- Ability to give informed consent or the availability of a surrogate who can consent on the patient's behalf.

Exclusion Criteria:

- Patients with subarachnoid or intracerebral hemorrhage
- Patients with transient ischemic attack (TIA)
- Patients with expected survival less than 6 months/discharged to hospice

Enrollment

The target enrollment will be 2,000 subjects. We will make the initial contact with up to 300 hospitals. With the expectation of approximately 75 participating sites, we anticipate an enrollment period of approximately 18 months.

Study Procedures

Screening:

At hospitalization, study personnel will screen for eligible patients according to the PROSPER study inclusion/exclusion criteria. Study eligibility will then be confirmed via medical record review prior to discharge. Sites will be trained and required to screen subjects according to the screening procedures for GWTG-Stroke. Those who choose to participate will be consented by site staff before discharge home. Throughout enrollment, the PROSPER team will review demographics and characteristics of patients to ensure a diverse population.

The follow-up Contact form will also be completed by the study coordinator at the time of enrollment using information provided by the patient at the time of enrollment. It includes comprehensive follow-up information for both the patient and two alternative contacts. Primary physician contact information will also be documented in the event that medical records are needed to be obtained. To assist with obtaining additional medical records a medical release form will also be obtained.

Baseline Data Collection

Baseline data collection will be completed by the study coordinator at the time of hospitalization, using primarily inpatient medical records. All baseline data must be collected and submitted for every subject within 7 days of enrollment. All data collection forms must be clearly labeled with the site-assigned unique study identifier.

- The GWTG – Stroke data collection form (Appendix A) will be the primary baseline data source for the acute ischemic stroke admission in GWTG hospitals. These in-hospital variables (required variables printed in bold font) include the following: demographics, medical history, NIHSS on admission, presentation information, stroke symptoms, evaluation, and diagnoses, acute therapies, including thrombolytics and DVT prophylaxis, discharge medications/interventions for recurrent stroke risk reduction, treating physician specialty, and discharge status and destination.
- The GWTG acute ischemic stroke hospitalization data will be augmented by the addition of the Rankin Scale
- Subject consent
- Subject Contact /demographics/stroke form
- Medical Release
- Discharge Medications

Follow-up Data Collection

Patients will be contacted at 3 months and 6 months post-discharge via telephone interviews. Questionnaires will be administered by trained research personnel at the DCRI and will utilize standard scripts. The enrolled stroke survivor will be the targeted respondent for the questionnaire, although proxy interviews may be used when it is impossible to speak to the patient or when the information provided by the patient is deemed unreliable by an experienced interviewer. The frequency of proxy interviews will be monitored and every effort will be made to keep proxy rates to a minimum. Additionally, at the 3 month follow-up, interviewers will verify all current contact information in order to minimize the possibility of outdated contact information. Enrolling site coordinators and primary care providers will be used as a resource for updated information, if necessary.

Follow-up Questionnaire Content:

- Current medication regimen
- Discontinued medications
- Health Status
  - Physical functioning
  - Depression
  - Symptom checklist
  - Impact of stroke on physical function
  - Fatigue
  - Desired Health Outcomes
- Resource utilization (i.e., rehospitalizations and procedures)

	Screening / Enrollment	3 month	6 month
Responsibility assigned to:	**Site**	**DCRI**	**DCRI**
Informed Consent	**X**		
Confirmation of inclusion/exclusion criteria via medial record review	**X**		
Discharge Medication list	**X**		
Medical Release Form	**X**		
GWTG Stroke DCF including additional stroke and depression variables.	**X**		
Subject Contact /demographic/stroke variable form	**X**		
Subject telephone interview questionnaire		**X**	**X**

Ethical Considerations

Consent Process

Retrospective:

This portion of the study will perform secondary analysis of data previously collected; therefore we will neither recruit nor consent subjects. There is no direct patient contact for this portion of the study.

Prospective:

Participating sites will consent PROSPER participants while in-hospital. Clinical staff will provide the patient a summary of the project and its goals, and ask the patient to sign an informed consent prior to discharge. Each subject will be assigned a unique study identifier that will be confidentiality maintained throughout all of the data collection processes, including collection of baseline hospitalization and discharge information and follow-up interviews at 3 and 6 months.

Capacity to Give Consent

Retrospective:

This portion of the study will comprise secondary analysis of data previously collected; therefore we will neither recruit nor consent subjects. There is no direct patient contact for this portion of the study.

Prospective:

Patients who are determined to be clinically or cognitively incapable of giving informed consent according to their medical records will not be approached by local site personnel. The consenting process will allow authorized signature for those subjects that cannot physically sign consent.

Subject/Stroke Population/Site Education Mechanisms

Educational Forums

PROSPER will develop shared tools that can be disseminated to subjects and sites through webinars/AHA website and social media platforms. Tools will be developed using information on stroke care, self-management, personalized risk-prediction, and decision aids for long-term therapies that will more effectively empower stroke survivors to make treatment decisions based on their own values, preferences, and needs. After a tool has been developed, we will pilot test the tool with patients and care partners to assess relevance and user-friendliness prior to launch.

Risk/Benefit Assessment

Retrospective:

There is no physical risk to any participant submitted as part of a data registry or administrative dataset. The primary risk is potential loss of confidentiality and/or misuse of PHI. There are no direct benefits to the patient since these projects involve only secondary analyses of preexisting databases. Thus, participation in this study does not prospectively affect patients or their medical care. However, findings will provide key information on quality of care of stroke patients and the potential relationship with patient outcomes. Given the minimal risk

associated with inclusion in these databases, the anticipated benefits to increasing knowledge and improving patient outcomes outweigh this risk.

Although the GWTG-Stroke is a limited dataset, DCRI manages these data with the same rigor as those data with directly identifying information. Patient-level data will be password protected and only will be accessible to the statistical programmer and statisticians. All abstracts, presentations, or manuscripts developed from this research will use and report aggregate data; no subject identifiers will be used in the presentation of the results.

Prospective:

There are minimal risks for this study. The main risk is potential loss of confidentiality. However, the Coordinating Center has strict procedures in place to prevent loss of confidentiality. First, the contact information website will be housed on a DCRI server with robust firewall and router protection. All enrolled patients will be identified through mapping a unique study-specific identifier to patient-level data, including hospital, admission date, and date of birth.

Contact information for telephone interviews will be accessible only to specified interviewing personal via a password protected mechanism. Collected telephone interview data will be stored in separate tables using the unique study identifier, as the primary key. These data will not be tied to the PHI collected as part of the contact information. All interview data will be stored on a password protected server and adhere to DCRI electronic safeguards.

Statistical Considerations

PROSPER will apply statistical protocols with pre-specified inclusion/exclusion criteria, analytic plans and sensitivity analyses. The analytic framework for PROSPER will, in general, utilize a “causal inference method”, or propensity scoring methods, to compare the safety and effectiveness of two or more stroke prevention, treatment, and management strategies. Standardized difference will be used to assess the balance across compared groups with respect to potential confounding variables in propensity score analysis.

Our primary end point, “home time”, will be analyzed using a linear regression model with transformations as necessary. Time to event outcomes (e.g. time-to-death, time to readmission) will be analyzed using the Cox proportional hazard model. Based on the models, the Wald’s tests will be used to test the significance of the treatment effects. After fitting models, the marginal residuals from the model will be used to test the goodness-of-fit of the proportional hazards model, with special attention to the proportionality assumption. When this assumption is not supported by the data, possible treatment and time interactions and other possible time-dependent covariates will be used to account for this non-proportionality. The resulting p-values that are less than 5% will be considered evidence of significant marginal differences across the cohorts.

Dichotomous outcomes (e.g. mRS, death, readmission) and continuous outcomes (e.g. Barthel Index, home time as a continuous measure) will be analyzed using multivariate logistic regression and multivariable linear regression models. We will perform subgroup analyses and/or advanced statistical modeling to determine the possible interaction between the treatment and patient characteristics and estimate the heterogeneity of treatment effects to reflect the individualization of results from the analyses. Our analyses will also account for clustering of patients within hospitals using generalized estimating equations (GEE).

Retrospective Power Analysis:

Based on our other work and the overall anticipated sample size of 450,000 ischemic stroke records in the GWTG-Stroke between 2007 and 2012 to maintain >90% power for the majority of subgroup analyses

Prospective Power Analysis:

The prospective study population comprises 5,000 patients in the combined AVAIL and PROSPER call center datasets. Based on estimated sample sizes, we will have greater than 90% power to detect patient-reported outcome differences of 7% (oral anticoagulant analysis), 6% (statin analysis), and 8% (anti-depressant analysis) between treated and untreated groups.

Governance

Science and Publications Committee

The Publications Committee of PROSPER will include the investigative team as well as clinical and academic representatives from participating sites. The Publication Committee will function as an independent body of scientific and medical experts with the following charter:

a. The Publication Committee shall be responsible for the review and approval of analyses suggested by both internal and external investigators;

b. The Publication Committee shall read and constructively critique all abstracts and manuscripts prior to submission for presentation or publication;

c. The Publication Committee shall consider each manuscript proposal with due regard for the scientific merit of the proposed publication with the aim of promoting the dissemination of scientific and medical knowledge;

d. Decisions of the Publication Committee shall be by majority vote, and there shall be no restrictions on the topics or analytical approaches used in developing manuscripts and presentations, other than those imposed by the Publications Committee;

e. All manuscripts approved by the Publication Committee shall conform to the Uniform Requirements for Manuscript Submitted to Biomedical Journals, including, but not limited to the standards for authorship.

Executive Committee

TBD

Steering Committee

TBD

Appendix