“The Home INR Study (THINRS)”

Cooperative Studies Program #481

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David B. Matchar, MD
Co-Principal Proponent
Durham VAMC

Alan Jacobson, MD
Co-Principal Proponent
Loma Linda VAMC

Robert Edson, MA
Study Biostatistician
Palo Alto Cooperative Studies Program Coordinating Center

PRIVILEGED AND CONFIDENTIAL
For review by the Cooperative Studies Evaluation Committee
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<th>Name</th>
<th>Position</th>
<th>Address</th>
<th>Email Address</th>
</tr>
</thead>
<tbody>
<tr>
<td>David B. Matchar, MD</td>
<td>Co-Principal Proponent</td>
<td>DUMC Div Of Gen Med, Dept Of Med 2200 W Main St Suite 230 P. O. Box 90527 Durham, NC 27710 <a href="mailto:david.matchar@duke.edu">david.matchar@duke.edu</a></td>
<td></td>
</tr>
<tr>
<td>Alan Jacobson, MD</td>
<td>Co-Principal Proponent</td>
<td>VAMC Cardiology (111C) 11201 Benton Street Loma Linda, CA 92357 <a href="mailto:Akjacobson@linkline.com">Akjacobson@linkline.com</a></td>
<td></td>
</tr>
<tr>
<td>Robert Edson, M.A.</td>
<td>Cooperative Studies Program Coordinating Center</td>
<td>VA Palo Alto Health Care System (151-K) 795 Willow Rd, Bldg. 205, Room 205 Menlo Park, CA 94025 <a href="mailto:Bob.edson@med.va.gov">Bob.edson@med.va.gov</a></td>
<td></td>
</tr>
<tr>
<td>Ciaran Phibbs, Ph.D.</td>
<td>Cooperative Studies Program Coordinating Center</td>
<td>Palo Alto VAMC (151-K) 795 Willow Rd. Menlo Park, CA 94025 <a href="mailto:cphibbs@stanford.edu">cphibbs@stanford.edu</a></td>
<td></td>
</tr>
<tr>
<td>Julia E. Vertrees, Pharm.D.,  BCPP</td>
<td>VA Cooperative Studies Program Clinical Research Pharmacy Coordinating Center 2401 Centre Ave., S.E. Albuquerque, NM 87106-4180 <a href="mailto:Julia.vertrees@csp.research.med.va.gov">Julia.vertrees@csp.research.med.va.gov</a></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Jack E. Ansell, M.D.</td>
<td>Dept. of Medicine</td>
<td>Boston University Medical Center 732 Harrison Avenue Boston, MA 02118 <a href="mailto:jack.ansell@bmc.org">jack.ansell@bmc.org</a></td>
<td></td>
</tr>
<tr>
<td>Michael Ezekowitz, MD</td>
<td>Director, Yale Clinical Trials Office</td>
<td>47 College St., Suite 202 Yale University New Haven, CT 06510 <a href="mailto:michael.ezekowitz@yale.edu">michael.ezekowitz@yale.edu</a></td>
<td></td>
</tr>
<tr>
<td>Stephan D. Fihn, M.D.</td>
<td>VA Puget Sound Health Care System (152)</td>
<td>1660 S. Columbian Way Seattle, WA 98108 <a href="mailto:sfihn@u.washington.edu">sfihn@u.washington.edu</a></td>
<td></td>
</tr>
<tr>
<td>Lou Fiore, M.D.</td>
<td>Hematology/Oncology</td>
<td>Boston VAMC 150 S. Huntington Avenue Jamaica Plain Boston, MA 02130 <a href="mailto:lfiore@bu.edu">lfiore@bu.edu</a></td>
<td></td>
</tr>
<tr>
<td>Frederick Rickles, M.D.</td>
<td>The George Washington Univ. Med. Center</td>
<td>2300 Eye Street, NW Ross Hall 712 Washington, D.C. 20037 <a href="mailto:resfr@gwumc.edu">resfr@gwumc.edu</a></td>
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### Abbreviations Used In This Document

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Full Form</th>
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<tr>
<td>AC</td>
<td>Anticoagulation</td>
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<td>ACS</td>
<td>Anticoagulation services</td>
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<td>AF</td>
<td>Atrial fibrillation</td>
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<td>CBC</td>
<td>Complete Blood Count</td>
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<tr>
<td>CSEC</td>
<td>Cooperative Studies Evaluation Committee</td>
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<td>CSP</td>
<td>Cooperative Studies Program</td>
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<td>CSPCC</td>
<td>Cooperative Studies Program Coordinating Center</td>
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<tr>
<td>DSMB</td>
<td>Data and Safety Monitoring Board</td>
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<tr>
<td>DVT</td>
<td>Deep venous thrombosis</td>
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<td>HQACM</td>
<td>High quality anticoagulation management</td>
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<tr>
<td>HSS</td>
<td>Human Subjects Subcommittee</td>
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<td>IDE</td>
<td>Investigational Device Exemption</td>
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<tr>
<td>INR</td>
<td>International Normalized Ratio</td>
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<td>MAST</td>
<td>Managing Anticoagulation Services Trial</td>
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<td>MI</td>
<td>Myocardial Infarction</td>
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<tr>
<td>MHV</td>
<td>Mechanical heart valves</td>
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<td>QOL</td>
<td>Quality of Life</td>
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<td>PE</td>
<td>Pulmonary embolism</td>
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<td>PST</td>
<td>Patient self-testing</td>
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<td>PT</td>
<td>Prothrombin time</td>
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<tr>
<td>RCT</td>
<td>Randomized controlled trial</td>
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<tr>
<td>SC</td>
<td>Study Coordinator</td>
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<td>SI</td>
<td>Site Investigator</td>
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<tr>
<td>TE</td>
<td>Thromboembolism</td>
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<td>TTR</td>
<td>Time in target range</td>
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<tr>
<td>VA</td>
<td>Department of Veterans Affairs</td>
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<td>WHO</td>
<td>World Health Organization</td>
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The CSP study is a trial of the clinical impact of Patient Self-Testing (PST) of prothrombin time by international normalized ratio (PT-INR or INR) with weekly testing compared to high quality anticoagulation management (HQACM) with conventional monthly testing. Sites will be VA Medical Centers with anticoagulation services (ACSs) with active rosters of more than 400 patients. This study will include subjects with atrial fibrillation (AF) and/or mechanical heart valve (MHV) who are expected to be anticoagulated indefinitely. The study will have two parts. Part 1 is a lead-in in which potential and consenting candidates for PST will be evaluated over a 2-4 week period for their ability to use the home monitoring meters. In Part 2, individuals capable of performing PST will be randomized (after separate consent) to one of two groups:

- HQACM with testing every 4 weeks and as indicated for out of range values, medication/clinical changes, or
- PST with testing every week and as indicated for out of range values, medication/clinical changes.

PST will involve the use of the ProTime® INR monitoring meter which is FDA approved for home use. The primary outcome measure will be event rates, defined as the percent of patients who have a stroke, major bleed, or die. The secondary outcome measures will be total time in range (TTR) (with and without adjustment for projected event risk), a loss function (derived from integrating the observed INR values over the distribution of projected outcome rate per INR value), other events (myocardial infarction (MI), non-stroke thromboembolism (TE), minor bleeds), competence and compliance with PST, satisfaction, AC associated quality of life (QOL), cost effectiveness, and ability to make dosing decisions. Sites will have to fulfill certain requirements to be eligible for participation.

To assess the relationship between frequency of testing and outcomes, a substudy is proposed in which several sites will randomize to 4 arms:

- HQACM with testing every 4 weeks and as indicated for out of range values, medication/clinical changes,
• PST with testing every 4 weeks and as indicated for out of range values, medication/clinical changes,
• PST with testing every week and as indicated for out of range values, medication/clinical changes, or
• PST with testing twice a week and as indicated for out of range values, medication/clinical changes.

The two additional arms (PST with testing every 4 weeks and PST with testing twice a week) will remain open until about 100 patients (a sample size sufficient to assess the impact of frequency on TTR [Samsa 2000]) have been enrolled in each. Note that the substudy is proposed to start at the beginning of the main study so that if CSP #481 terminates early due to the results of interim analysis, there will be sufficient data (at least one year of follow-up) to assess the impact of PST frequency on clinically important improvements in quality of AC as measured by TTR.

The study design includes one year of patient accrual and a minimum of two years of follow-up with those enrolled early in the study being followed for up to 4.75 years. The study will involve 3200 patients and 32 sites.
I. INTRODUCTION

A. Primary Objectives

The primary objective of the Veterans Affairs Cooperative Studies Program Home INR Testing study is to compare anticoagulation management with frequent patient self testing (PST) of prothrombin time (PT) using a home monitoring meter to high quality anticoagulation management (HQACM) implemented by an anticoagulation service (ACS) with conventional monitoring at two years on major health outcomes: stroke, major bleed, and mortality.

B. Secondary Objectives

The secondary objectives of the study are to:

- Compare PST versus HQACM for the following secondary outcome variables:
  (a) Time in target range (TTR), both with and without adjustment for event risk, based on Prothrombin Time standardized to the International Normalized Ratio (PT-INR which will be referred to as INR);
  (b) Loss function (i.e., derived from integrating the observed INR values over the distribution of projected outcome rate per INR value);
  (c) Events other than those for the primary outcome (e.g., minor bleeds);
  (d) Competence and compliance with PST (for the PST group only);
  (e) Satisfaction with care (preferred management strategy);
  (f) AC-related quality of life (QOL);
  (g) Cost-effectiveness; and
  (h) Ability to make dosing decisions.

- Identify subject characteristics that predict proper use of INR self-monitoring meters.

- Identify categories of patients and indications for which PST is most clinically effective and cost effective.

- In a substudy, determine the relationship between frequency of testing and each of the primary and secondary outcomes described above. (The substudy sample size is...
sufficient to assess the effect of test frequency on TTR, but may be too small to provide sufficient statistical power for other study outcomes.)

II. BACKGROUND

A. Potential Benefits of Patient Self Testing in Anticoagulation Management

Anticoagulation (AC) with warfarin has been shown to reduce the risk of thromboembolism (TE) in a variety of applications. AC is effective for prophylaxis of venous thrombosis in high-risk surgery, treatment of venous thrombosis and pulmonary embolism, and prevention of systemic embolism in patients with acute myocardial infarction (MI), valvular heart disease, atrial fibrillation (AF), tissue heart valves, or mechanical heart valves (MHVs). Recent research also suggests a potentially major role in secondary prevention of MI [Hirsh, 1998].

Despite the compelling evidence supporting the value of AC and the importance of high quality AC, warfarin remains underused and, for those receiving treatment, dosing is often suboptimal [Matchar, 2000]. Both issues are critically important; however, given that warfarin has a narrow therapeutic index, the primary concern in providing AC is quality.

Management of AC is not a trivial task, and numerous barriers to optimal AC management have been identified [Samsa, 1998]. Two examples are (1) engaging patients to participate in treatment and (2) maintaining systematic supervision of AC treatment [including the performance and follow-up of PT, as measured in INR]. Patient participation is essential because effective treatment requires a) awareness of diet, interacting medications, and complex dosing regimens; b) recognizing signs of adverse events; and c) attending clinic appointments for monitoring and assessments. Regular contact with the healthcare provider is required to ensure patient adherence to a self-testing or self-management protocol and prompt responses to out-of-range INR values.

Several approaches have been recommended to improve the quality of AC. One approach is an anticoagulation service (ACS). A detail- and time-intensive activity such
as high-quality AC management (HQACM) is difficult in the hectic environment of the busy outpatient clinic. An ACS allows the busy physician to delegate the day-to-day details of AC management to another provider (e.g., a pharmacist or nurse) who is able to give his or her complete attention to AC.

Another approach to improving the quality of AC is to engage the patient more directly in the process of care. One way to do this, illustrated by modern strategies for diabetes care, is by incorporating a home-monitoring system into a comprehensive treatment plan. Patient self-testing (PST) involves patients performing their own blood testing (typically, using a finger-stick blood analyzer). In patient self-management (PSM), patients not only perform their own testing, but also make most or all of their own dosage adjustments. In general, a) patients are allowed to practice PST or PSM only after completing a comprehensive training program; b) dosage adjustments are made according to a PSM Protocol/Algorithm approved by the provider; and c) test results, dosing and other pertinent information are forwarded (e.g., by telephone or modem) to the provider on a regular basis. PST is the most limited form of PSM on the continuum of potential uses of home INR monitors [Anderson, 1993; Weibert, 1989; Ansell, 1999].

A few randomized trials of PST/PSM versus HQACM / usual care have been reported in the literature. In the European Study of Patient Self-Management of Oral Anticoagulation, Sawicki studied 165 patients presenting to 5 departments specializing in the management of anticoagulation and, thus, presumably providing HQACM. [Sawicki, 1999] (The failure to provide a detailed description of the process of care in the controls, and thus explicitly demonstrate that the controls represent HQACM rather than usual care, is a shortcoming of this study as well as most of the other European trials.) All patients were new to the centers (although not necessarily new to anticoagulation) and required life-long anticoagulation therapy. Most had mechanical heart valves. The intervention group (n=83) included PST/PSM at a recommended testing interval of 1-2 times per week, while the control group (n=82) involved visits to family practitioners or an outpatient clinic at a recommended interval of every 2 weeks. The outcome variable was the percentage of patients within target range at various snapshots in time (i.e., a variant of the cross-section of the files approach) [Rosendaal, PRIVILEGED AND CONFIDENTIAL;5/18/2006; 5
At 6 months, 53% of observations in the PST/PSM group were within target range versus 43% in the controls -- this in comparison with 29% and 36%, respectively, at baseline. The PST/PSM group also showed an improvement in anticoagulation-related quality of life in comparison with the controls.

White identified 50 outpatients discharged from 2 hospitals in California, who were started on warfarin for the first time and had not yet achieved stable anticoagulation. [White, 1989] Of the 50, 26 were randomized to PST (with tests twice per week, dosage adjustments and other management by internists, and most patient contact through the telephone), and 24 were randomized to HQACM (managed by an ACS, with tests once per week). Patients had various indications for anticoagulation, mostly deep-vein thrombosis, and were followed for 8 weeks after the initiation of therapy. Using a narrow target range 77% and 50% of observations, respectively, were in range; these figures became 93% and 75% when a wider target range was applied.

Horstkotte describes a randomized trial following 150 German patients with new mechanical heart valves for approximately 18 months post-surgery. 75 patients received PST/PSM with a recommended testing interval of 3 days, while 75 patients received physician care (assumed but not demonstrated to be HQACM) without special testing intervals. [Horstkotte, 1998] Actual testing intervals were 4 and 19 days, respectively. Approximately 43% and 22% of INR measurements, respectively, were within a narrow definition of the target range; these figures became 92% and 59% when the target range was expanded. Statistically significant differences were observed in TE (0.9% versus 3.6%) and bleeding complications (4.5% versus 10.9%). Major and minor bleeding complications were not reported separately.

In preliminary results (i.e., first 600 patients completing the final follow-up examination) from the Early Self-Controlled Anticoagulation Trial, which follows approximately 1,200 European mechanical heart valve patients for 2 years post-surgery, the PSM group tested approximately 4 times per month in comparison with the controls (conventional physician management without special testing intervals -- again, assumed but not demonstrated to be HQACM) who tested 1.5 times per month. The proportions of measurements within target range were 78% and 60%, and the annual
TE rates were 1.2% and 2.1%, respectively. [Koertke, 1999] Almost 92% of participants who began PST/PSM were willing and able to continue to self-manage their anticoagulation throughout the study.

Although not definitive (e.g., all patients proceeded from long to short time intervals, and the generalizability of the patient population is uncertain), Horstkotte's experiment provides perhaps the most direct evidence available in support of the benefits of increased frequency of testing. The literature also includes two case-control studies, each of which followed a group of patients undergoing self-management, then attempted (through matching) to select a comparable group of controls. Hasenkam compared 20 patients with new MHVs to a similar number of controls (matched, in order of priority, by valve position, valve type, age, sex, and time of operation). [Hasenkam, 1997] All patients in the PST/PSM group lived within 100 kilometers of the hospital, and were judged to be likely to comply with a PSM program as determined by an initial interview. Intervention patients tested INRs weekly. Controls were tested less frequently. The TTR was 77% versus 53%, respectively. Ansell compared 20 PST/PSM patients with an equal number of controls selected from the same university-based ACS. [Ansell, 1995] Most PST/PSM patients were selected as particularly likely to be compliant with a self-management regimen. Testing intervals were 14 days for PST/PSM and 16 days for HQACM, respectively, and proportions of measurements within target range were 89% and 66%. Sixteen of 17 PSM patients preferred PST/PSM to HQACM. Both case-control studies are potentially biased in the sense that most PST/PSM patients were selected by interview as likely to be particularly compliant and/or otherwise competent in the absence of performing similar interviews to select the controls; thus the observed differences can not be definitively attributed to PST/PSM. Nevertheless, the results are consistent with extant randomized clinical trials (RCTs).

Other studies in the literature include an uncontrolled report by Bernardo [Bernardo, 1996] and an abstract by Beyth describing a RCT comparing PST (with dosing decisions made by providers according to protocol and including additional components of a behavioral intervention) with usual care, the results favoring self-testing, albeit only during the first 6 months of follow-up. [Beyth, 1997].
B. Special Design Issues

1. Selection of Control Group

HQACM is characterized by, among other features, use of an evidence-based dosing protocol, excellent communication and follow-up systems, and regular patient education. HQACM could utilize a point-of-care blood analyzer in order to increase efficiency within the office or clinic, but would not include either PST or PSM. It is important to note that HQACM could be provided by either an ACS or by individual physicians - the important point is not the specific model of care, but rather that there is some sort of demonstration that the providers have systems in place to achieve the goals of anticoagulation management. Because an ACS typically involves the development and elucidation of various protocols (e.g., protocols for dosage adjustment, protocols for patient contact in case of emergencies, etc.) this demonstration is often implicit in the implementation of the ACS. Physician management, however, requires additional information to help the reader distinguish between HQACM and somewhat haphazard usual care.

2. Selection of Outcome Measures

The anticoagulation literature primarily utilizes three types of outcome measures: (1) clinical event rates; (2) proportion of INR values within target range; and (3) time in target range (TTR).

Event rates are defined to be the number of clinically important events per patient-year of follow-up. These clinical events, including stroke, TE, major bleed, minor bleed, MI, and death are not operationalized in the same way from study to study. This is particularly true for the definition of the threshold above which a bleeding incident is classified as major rather than minor. For purposes of a study, the events to include in an aggregate measure should all be serious and likely to be affected by treatment (either positively or negatively); for CSP #481 the candidate events are TE (primarily strokes), major bleeds (focusing on those most likely to be life threatening and thus comparable to a stroke), and death. MI is not included in the primary endpoint (but is a secondary endpoint) because in a general population of anticoagulated patients, MI is
not clearly affected by warfarin treatment. Death is included because, except for the CAFA study [Connolly, 1991] which also failed to demonstrate statistically significant stroke prevention benefit, warfarin trials consistently show reduced mortality (not otherwise attributed to TE) for subjects receiving warfarin (relative risk is approximately 0.57 for AF patients and 0.71 for post MI patients). [Matchar, 1994]

The proportion of INR values within target range is defined as the number of INRs within target range divided by the number of PT tests. The resulting figure is simple to calculate but biased. That is, the figure is affected by the tendency for physicians to perform repeated tests soon after an out-of-range INR (e.g., to verify the initial INR or assess the effect of a dosage adjustment). [Rosendaal, 1993] It can be demonstrated that this bias increases as the interval between tests increases. For monthly testing intervals, empirical data suggests that the magnitude of the bias is approximately 10% -- that is, percentage of in-range PT tests is approximately 90% of the TTR (data not shown) [Rosendaal, 1993; Samsa, 2000; Matchar, 2000]. The “cross-section of the files” method is a variation of the above. In this method, a given date is selected, and the calculation of the proportion of INRs within target range utilizes the most recent INR value for each patient. The “cross-section of the files” method is unbiased, but inefficient as it fails to utilize test results between the assessment dates.

The TTR involves first linearly interpolating between observed test values in order to extrapolate data points on a daily basis, then defining the TTR as the number of patient-days of follow-up which were within target range divided by the total number of patient-days included in the follow-up period. [Rosendaal, 1993] A deficiency of TTR is that it depends upon the choice of target INR range -- in particular, expanding the target range will increase the TTR, even in the absence of any actual improvements in quality of anticoagulation management. Another deficiency of TTR is that it treats small departures from target range as identical to large departures (i.e., the former having little impact on event rates but the latter having a large impact once the margin of safety is exceeded). One potential remedy for both deficiencies is to also report time highly out-of-range. Another option is to report a loss function, which applies a penalty that increases with the distance from the INR target. (One particularly natural loss function is the event rate that is predicted based upon the observed INR.)
In comparing the various outcome measures, we note that event rates are the outcomes that are ultimately of interest, while TTR and proportion of in-range tests are intermediate outcomes that may be more or less highly correlated with these event rates. Thus, all things being equal, event rates are the outcome of choice. (Because the proportion of in-range tests is both biased and contains less information than TTR, we will now limit consideration to clinical event rates and TTR.)

However, all things are not necessarily equal. In particular, there are two crucial differences between TTR and event rates: **statistical precision** and **decisional impact**. Even in high-risk populations, significant clinical events such as TE and major bleeding will be relatively uncommon occurrences, for example, in 5% of patients per year or less. (Note that event rates in HQACM should be lower than those observed in typical epidemiologic cohorts and/or other manifestations of usual care.) On the other hand, INRs tend to be within their target range approximately half of the time, [Ansell, 1998] the value at which a proportion (such as TTR) has its largest possible standard deviation. The important implication is that the sample size for a RCT using event rates as the primary outcome would be have to be much larger (perhaps by a factor of 10) than the sample size for a comparable trial using TTR. A paper (Samsa, 2000) provides an example of how the sample size for an event rate study compares to one using TTR as the primary outcome.

Various peer-reviewed studies have utilized TTR as their primary outcome measure. Most particularly, the Managing Anticoagulation Services Trial (MAST), [Samsa, 1998] the largest RCT to date of ACS (effectively HQACM) versus usual care as provided in the community is using TTR as its primary outcome, with this design decision having been endorsed by an external review panel of the Agency for Health Care Policy and Research.

Because of issues of sample size, a reasonable policy would be to use as the primary outcome TTR rather than event rates so long as the relationship between TTR and event rates is sufficiently strong. In fact, a strong relationship between TTR and event rates is consistent not only with the pharmacokinetics of warfarin (and other anticoagulants) and consensus statements, [Hirsh, 1998] but has also been observed
across a large number of studies with different patient populations, different target ranges, and different scales for measuring intensity of anticoagulation (i.e., PT, PTR, and INR). A paper (Samsa, 2000) provides details for a representative, albeit not necessarily exhaustive, set of studies.

The second crucial difference between TTR and event rates is the decisional impact of a study based on the results. This has been the subject of extensive debate by the CSP #481 Planning Committee. The consensus of this group is that while both TTR and event rates will provide sufficient data for important clinical and policy decisions within the VA, an event rate study would be viewed as more definitive and thus persuasive to the relevant community of decision makers. In view of all of the above, it has been recommended that the design of CSP #481 be based on clinical events as the primary outcome measure, and TTR (with and without adjustment based on predicted event risk) as the principal secondary outcome. Further, to minimize the risk of a negative study, an interim analysis based on aggregate events is recommended to determine whether the study will be adequately powered for event rates. Should this interim analysis suggest inadequate power at the original projected sample size, the study can be terminated at the interim point since it is certain to be adequately powered to assess study results based on TTR.

3. Mapping TTR to event rates

Although neither the strength nor the shape of the relationship between TTR and event rates is in question (i.e., the function can be modeled as approximately exponential with event rates becoming noticeably higher as the distance from the target range increases), there remains the question of how precisely the exact risk of clinical events can be determined for a given patient in a specific INR range. Two methodological difficulties complicate this task: the effect of other patient characteristics and the level of detail provided by the literature.

Regarding patient characteristics, it is well-known that a large number of factors (e.g., age, indication for anticoagulation, previous history of TE / bleeding) can affect a patients risk of clinical events [Levine, 1998]. Although point estimates of the regression
coefficients associated with many of these patient characteristics have been described, [Fihn, 1993], particularly in selected subpopulations such as patients with mechanical heart valves, [van der Meer, 1993] these estimates are not necessarily generalizable nor are they always associated with a high degree of precision.

A second difficulty in mapping INRs to event rates involves the level of detail with which data are typically reported. For example, in the literature INRs are often classified into very few categories (e.g., below target range, within range, above range). However, the larger the category the more the guesswork in extrapolating a mean INR within that category, and the greater the error introduced into the mapping of INRs to clinical event rates. By implication, generating a mathematical model mapping INRs to event rates requires a large cohort of patients as well as access to raw data or a report using a large number of INR categories.

Figure 1 (Observed and Predicted Relationship Between INR and Clinical Events) illustrates the derivation of a relationship, using the data on a cohort of mechanical heart valve patients reported by Cannegieter (i.e., a large cohort reporting data using many INR categories). [Cannegieter, 1995] Applying logistic regression (and approximating data values based upon figures from Cannegieter’s paper), we estimate that, for a typical patient, the relationship between INR and TE is \( Y = -0.73 - 1.17 \times \text{INR} \) and the relationship between INR and major bleeding is \( Y = -8.84 + 0.83 \times \text{INR} \), where \( Y \) denotes the natural logarithm of the probability of that type of an event occurring during a typical patient-year of follow-up. By visual inspection, these models fit the data well, with the possible exception of the most extreme categories, which had relatively few patient-years of follow-up and thus were particularly "noisy."
Figure 1: Observed and Predicted Relationship Between INR and Clinical Events
In summary, although it is relatively straightforward to create an internally consistent rule for assigning risk of clinical events based upon patient characteristics and observed INR, such a rule runs the risk of being miscalibrated (i.e., either consistently over- or under-estimating the rate of clinical events for a given INR category). While acknowledging that this problem exists, we argue that its implications for a RCT are not serious so long as the relationship between INR, patient characteristics, and outcomes is specified before data analysis begins. That is, so long as it is specified beforehand, any tendency for the rule to systematically over- or under-estimate clinical event rates should affect both the intervention and control groups more or less equally, and thus any errors will tend to be similar. In other words, the TTR results are clinically meaningful and can be used to assess whether PST is clinically superior to HQACM.

C. Impacts in the VA

For the past decade, portable monitors have been available to test INR. In 1997 the FDA approved the first of these meters for home use. Over the next several years, it is expected that four to five such meters will also be approved. Because home INR monitors have the potential to improve the safety, quality, and convenience of chronic anticoagulation, there is likely to be a call from providers, patients, and manufacturers to make home INR monitors available to patients in the VA.

There is limited evidence [Ansell, 1995, 1996; Kaatz, 1995; McCurdy, 1992; White, 1989; van den Besselaar, 1995] that these meters can be used accurately and reliably, and that they can improve the quality of anticoagulation. However, these studies have been small, involving patients with selected characteristics (e.g., just MHV patients), and have not been shown to be cost-effective in typical settings. Even if proven in a non-VA clinical trial, it is not clear that the results will be generalizable to the VA population. Concerns include:

- differences in the proportion of VA patients who will be able to effectively use the meters (based on factors such as education level, cognitive ability, manual dexterity),
• differences in the nature of the conditions for which the patient is receiving warfarin, and
• differences in the effectiveness of conventional anticoagulation services in the VA, compared to non-VA settings (such as availability of rapid turn-around laboratory results, distance between patient and anticoagulation clinic).

III. RESEARCH METHODS

A. Summary

CSP #481 is a trial of the clinical impact of PST with weekly testing compared to HQACM with conventional testing every four weeks (Figure 2). Sites will be VA Medical Centers with ACSs with active rosters of more than 400 patients. This study will include subjects with AF and/or MHV who are expected to be anticoagulated indefinitely. The study will have two parts. Part 1 is a lead-in during which consenting subjects will be evaluated over a 2-4 week period for their ability to properly use the home monitoring meters and perform PST.

PST will involve the use of the ProTime® INR monitoring meters that are FDA approved for home use. The primary outcome measure will be event rates, defined as stroke, major bleed, and death. The secondary outcome measures will be TTR (with and without adjustment for event risk), loss function (i.e., derived from integrating the observed INR values over the distribution of outcomes per INR value), other events (MI, non-stroke TE, minor bleeds), competence and compliance with PST, satisfaction with care, AC associated QOL, cost effectiveness, and ability to make dosing decisions. Sites will have to fulfill certain requirements to be eligible for participation.

In Part 2, individuals capable of performing PST will be randomized (after separate consent) with equal allocation to one of two groups:
• HQACM with testing every 4 weeks and as indicated for out of range values, medication/clinical changes, or
• PST with testing every week and as indicated for out of range values, medication/clinical changes.
To assess the relationship between frequency of testing and outcomes, a substudy (Figure 3) is proposed in which several sites will randomize to 4 arms:

- HQACM with testing every 4 weeks and as indicated for out of range values, medication/clinical changes (assigned to 1/2 of the patients),
- PST with testing every 4 weeks and as indicated for out of range values, medication/clinical changes (assigned to 1/6 of the patients),
- PST with testing every week and as indicated for out of range values, medication/clinical changes (assigned to 1/6 of the patients), or
- PST with testing twice a week and as indicated for out of range values, medication/clinical changes (assigned to 1/6 of the patients).

The two additional arms (PST with testing every 4 weeks and PST with testing twice a week) will remain open until about 100 patients (a sample size sufficient to assess the impact of frequency on TTR [Samsa, 2000]) have been enrolled in each. Note that the substudy is proposed to start at the beginning of the main study so that if CSP #481 terminates early due to the results of interim analysis, there will be sufficient data (at least one year of follow-up for all patients in the substudy) to assess the impact of PST frequency on clinically important improvements in quality of AC as measured by TTR.

The study design includes one year of patient accrual and a minimum of two years of follow-up with those enrolled early in the study being followed for up to 4.75 years. The study will involve 3200 patients and 32 sites.
Figure 2: Main Study Design

Screening, Week 0

PST Training, Week 1-3

Part 1 Competency Assessment, Week

Part 2 Baseline, Month 0

If entry criteria met

HQACM (N = 1600)

PST (N = 1600)

Part 2 Post-Baseline, Month 0

Cycle
N = 1

Part 2 Protocol follow-up visit, Month 3

Cycle
N = n

Part 2 Protocol follow-up visit, Month 3n

Cycle
N = 8 to 19

Part 2 Closeout/end of study visit, Month 24-57

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Figure 3: Substudy Design

**Part 2 Baseline, Month 0**

If entry criteria met.

1/2

**Randomization, stage 1**

1/2

**HQACM**

**PST**

1/3

1/3

1/3

**Randomization, stage 2**

**Part 2 Post-Baseline, Month 0**

**Cycle N = 1**

Part 2 Protocol follow-up visit, Month 3

**Cycle N = n**

Part 2 Protocol follow-up visit, Month 3n

**Cycle N = 8 to 19**

Part 2 Closeout/end of study visit, Month 24-57
B. Study Design

1. PART 1
   a. Subjects. This study will include AC patients with AF and/or MHV who are expected to be on AC indefinitely and will include patients for whom AC was or was not recently initiated (defined as less than or greater than three (3) months when identified as study candidates).
   b. Subject enrollment and eligibility. Most entry criteria will be checked during Part 1. All items are checked at the screening visit. To be enrolled in this study, patients must
      (1) have AF and/or a MHV;
      (2) be scheduled to receive warfarin indefinitely (operationally defined as until the study ends; 2-3 years);
      (3) be using warfarin according to the criteria described in the Coumadin package insert (no off-label uses);
      (4) be expected to survive for the duration of the study;
      (5) not be suffering from intracranial bleeding (intracranial hemorrhage, subarachnoid hemorrhage, hemorrhagic stroke) or any other contraindication described in the Coumadin package insert;
      (6) be willing or have a caregiver willing to perform PST;
      (7) be willing to be randomized;
      (8) possess adequate cognitive and language skills to follow the protocol and all related instructions, or have a caregiver who has these skills;
      (9) be willing to participate for the full duration of Parts 1 and 2 (25-37 months), and if needed, his/her caregiver is also willing;
      (10) sign the informed consent form for Part 1 and HIPAA authorization form (if needed, the caregiver must also sign a consent form and HIPAA authorization form); and
      (11) not be enrolled in another randomized clinical trial that involves a drug or meter intervention. The Cooperative Studies Program
Coordinating Center (CSPCC) may consider exemptions to this rule on a case-by-case basis.

c. Recruitment. Potential subjects will be identified from both prevalent cases (patients receiving services from the ACS) and incident cases (patients referred to the local ACS as well as those on monthly downloads of pharmacy lists). If the patient is judged likely to satisfy eligibility criteria, the patient will be approached by the Study Coordinator (with verbal approval of the patient’s referring physician). Upon obtaining the patient’s (and, if needed, the caregiver’s) informed consent for Part 1, he/she will be scheduled for a screening visit, during which an evaluation will be performed. A PST training visit will be scheduled for 1 week following the screening visit during which time the patient (and, if needed, the caregiver) will receive, individually or in a group session, basic AC training as well as training on use of the monitoring meter. Two weeks following the training, the patient (and caregiver, if needed) will have a visit to access competency in their use of the monitor. If deemed acceptable, the patient is eligible to participate in Part 2. If not, the patient/caregiver may repeat training and follow-up for an additional two weeks and be re-evaluated for participation in Part 2.

Subjects/caregivers may have unscheduled visits with the ACS Manager or Study Coordinator as needed. Subjects/caregivers will be given a copy of the schedule and the phone numbers of the ACS Manager and Study Coordinator. Subjects/caregivers will be encouraged to call for all protocol and non-protocol questions; for non-protocol medical questions, appropriate referral (e.g., ACS Manager, primary care provider) will be offered.

At the end of Part 1, the monitor will be retrieved from the subject/caregivers. Individuals evidently capable of using the monitor will be invited to participate in the randomized clinical trial (Part 2); the others will be ineligible to continue in CSP #481.
2. PART 2
a. Subjects. To participate in Part 2, the subject/caregiver must sign the Part 2 consent form, indicating that he/she is willing to be randomized.
b. Strata. Randomization will be stratified by site, duration of AC, and indication for AC. The strata are enumerated in Table 1.

Table 1: Strata for Randomization

<table>
<thead>
<tr>
<th>STRATUM</th>
<th>SITE</th>
<th>DURATION OF AC</th>
<th>INDICATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1</td>
<td>&lt; 3 months</td>
<td>AF</td>
</tr>
<tr>
<td>2</td>
<td>1</td>
<td>&lt; 3 months</td>
<td>MHV or AF and MHV</td>
</tr>
<tr>
<td>3</td>
<td>1</td>
<td>≥ 3 months</td>
<td>AF</td>
</tr>
<tr>
<td>4</td>
<td>1</td>
<td>≥ 3 months</td>
<td>MHV or AF and MHV</td>
</tr>
<tr>
<td>...</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>128</td>
<td>32</td>
<td>≥ 3 months</td>
<td>MHV or AF and MHV</td>
</tr>
</tbody>
</table>
After confirming eligibility, randomization will be performed as described. Subjects randomized to HQACM will have conventional visits scheduled. Whether assigned to the HQACM or PST groups, the Study Coordinator will arrange and perform face-to-face Protocol Follow-up Visits every three months.

These follow-up contacts are in addition to any visits otherwise scheduled for subjects in the HQACM group, or any unscheduled visits deemed necessary by the ACS Manager. Subjects will be given a copy of the schedule and the phone numbers of the ACS Manager and Study Coordinator. Subjects will be encouraged to call for all protocol and non-protocol questions; for non-protocol medical questions, appropriate referral (e.g., ACS Manager, primary care provider) will be offered.

3. Sites
To participate in this study, a site must:
(a) have an active roster of at least 400 patients receiving AC;
(b) have a computerized tracking system that allows new patients to be identified and existing patients to be stratified by indication for AC and duration of AC;
(c) have sufficient numbers of patients within the strata defined above;
(d) be willing to randomize subjects;
(e) demonstrate conformance to AC performance standards. Sites that are unable to maintain the CSP Study standards of HQACM (see Appendix A) will not be eligible to participate.
(f) be willing to treat all subjects (including those not receiving PST) according to the CSP Study Protocol; and
(g) be able to support PST (willingness and ability to perform patient training, etc.)

4. Intervention
Patients/caregivers enrolled in Part 2 will have demonstrated a basic level of competency with PST. Follow-up visits are designated to assess the quality of patient/caregiver ongoing performance. Significant deviations in quality of
PST relative to Figure 4 will be cause for withholding PST and, if necessary, withdrawal of the monitor and reversion to HQACM. Note that based on the intention-to-treat such patients will be evaluated with the PST group.

a. Method of treatment. Subjects/caregivers enrolled in Part 2 of the study will be randomized to the control intervention or to one of the PST interventions. The control intervention is designated HQACM. HQACM is AC care provided according to accepted functional definitions established by the Managing Anticoagulation Services Trial (MAST), based on work of the Anticoagulation Forum (Appendix A). The basic elements of HQACM are:

- a designated ACS Manager responsible for monitoring and follow-up of a panel of AC patients;
- INR tests are done by a central laboratory or point-of-care system using a plasma based system with commercially prepared thromboplastin (which may have variable sensitivities)
- standard records (a computer record-keeping system such as CoumaCare®);
- a manual of operation based on the MAST ACS Operations Manual (Appendix B) and consistent with the Coumadin package insert;
- standardized patient AC education; and
- communication with the patient’s primary provider.

The manual of operation for the ACS will include a recommendation that INR be monitored every 4 weeks, when stable.

PST subjects/caregivers will receive the same standardized AC education as HQACM subjects. In addition, most PST subjects will receive PST with monitoring every week, when stable. A subset of patients at selected sites will receive PST either twice a week or once every 4 weeks. The subject will be advised to monitor out-of-range values in a manner consistent with HQACM. Patients will receive additional cuvettes for this use.
Figure 4: Flowchart for Strip Wastage and Competency Assessment
b. Description of Monitoring System

1. System Description

Traditional PT INR testing has been performed on blood samples that have been collected by venipuncture into citrated tubes that prevent blood from clotting. These tubes are spun in a centrifuge to separate the plasma from the cellular elements. The plasma sample is then processed in a large automated instrument that adds a laboratory reagent, thromboplastin, to the sample. Thromboplastin triggers the formation of a blood clot and the PT is the number of seconds that it takes for a clot to form after thromboplastin has been added to the plasma sample. There is a wide difference in the ability of different commercial thromboplastin preparations to stimulate the formation of clotting resulting in significant variation between laboratories utilizing different thromboplastin reagents and coagulation instruments. In an attempt to reduce the variation between test systems, the WHO has recommended and most laboratories have adopted the INR (International Normalized Ratio) method of reporting the PT. The INR is a mathematical modification of the raw PT into the PT that would have been obtained had the WHO standard thromboplastin been utilized in the testing. While this has resulted in a significant reduction in the amount of variation between laboratories and test systems, it is not perfect and some variation remains.

In the mid 1980’s, small portable meters were developed that were capable of performing the PT test on fingerstick samples of whole blood utilizing disposable test strips similar to those used by diabetics in the testing of blood sugar. Three meters had been cleared by the FDA for patient home use by the end of 1999 and at least 2 additional meters were undergoing trials for FDA evaluation. Similar to traditional methods, these meters also utilize a thromboplastin to trigger clot formation. However, because they perform the test on a sample of whole blood, rather than citrated plasma, the actual number of seconds for clotting to occur may be different and therefore the meters perform a mathematical modification based on the result of extensive calibration comparisons to standardized methods. The meters are capable of reporting the results as either the PT in seconds or as an INR.
The method of determining that a clot has formed differs between each meter. There are also differences between meters in testing procedures, sample application, and user interfaces. Despite design and interface differences, however, the meters are in general more similar than different and all provide results that are clinically equivalent to a central laboratory (based on the fact that all meters successfully completed the FDA approval process and on the Principal Proponents' personal observations).

The most significant difference between meters is the manner in which they handle quality control. In the central laboratory, two levels of quality control solutions are utilized on at least a daily basis. The first level of quality control is a known solution that is expected to give a PT result similar to a normal person not on any blood thinners. The second level of quality control is a known solution that is expected to give a PT result similar to a person receiving therapeutic intensity warfarin therapy. One group of meters relies on the use of external liquid solutions to provide the two levels of quality control. The drawback is that this requires the use of two test strips for the performance of the quality control and has resulted in some controversy as to how frequently quality control should be performed. The other group of meters relies on “on-board” quality control. This requires a more complex test strip that is capable of performing both levels of quality control at the same time as the PT testing. The test strip with on-board quality control is more complex to design and produce and often requires a larger blood sample but provides the advantage of both levels of quality control with every test without consuming the time and test strip resources that external liquid quality control requires. However, both types of meters are commercially available in the United States and patients have repeatedly demonstrated the ability to competently utilize either type of meter.

The general recommendation for warfarin monitoring to be performed once every 4 to 6 weeks is not based on pharmacokinetics nor clotting factor half-lives but rather by practical constraints of access and cost balance against complications. The home INR monitors provide the potential for improved access to testing which for the first time provides a feasible method to increase the frequency of PT testing at a reasonable cost. In addition, for those patients who have testing performed at more than one laboratory
due to travel or other requirements, they now have the potential to have all their testing performed on the same system, thereby removing the residual variation between laboratories which the INR does not resolve.

2. Intended Use. The INR monitors used in CSP #481 are FDA approved for the following:
   a) point-of-care/physician’s office laboratory personnel, and
   b) lay persons receiving oral anticoagulation therapy who perform self-testing.

3. Accountability for Monitors and Cuvettes. Upon completion of the study, all monitors and unused cuvettes will be returned to CSP unless it is determined that CSP has no use for these materials. In that case, the equipment and supplies will be disposed of in accordance with the regulations of the Regional Research Equipment Program.

4. Assessment of Compliance. Compliance with the use of the meter will be assessed by counting cuvettes, review of phone system data, and by patient diary.

5. Occupational Safety. Universal precautions for handling blood and blood products will be observed throughout the study. All blood samples and materials coming in contact with blood samples will be treated as potentially biohazardous and handled accordingly.

6. Concomitant Medication/Treatment. Patients will be required to avoid use of home monitoring meters other than the meter provided as part of the study. All other aspects of medication and treatment will be unrestricted.

C. Outcome Measurements

Clinical measures are classified as follows:

1. Primary clinical outcome measures
   a) Stroke (as defined in Table 5)
   b) Major bleed (as defined in Table 5)
   c) Death

2. Secondary clinical outcome measures
   a) INR TTR (with and without adjustment for event risk)
(b) loss function
(c) other events
(d) Competence and compliance with monitor use
(e) Satisfaction (using the Duke Anticoagulation Satisfaction Scale or DASS [Samsa et al 2002])
(f) AC-associated QOL (using the Health Utilities Index or HUI), and
(g) Cost effectiveness

3. Potential explanatory variables

(a) Risk factors for TE
   • History of stroke, TIA, or TE
   • Known clotting abnormality
   • Atrial fibrillation (AF)
   • Diabetes
   • Hypertension
   • Smoking history
(b) Risk factors for bleed
   • History of bleed
   • History of fall with injury
   • Unstable walking
   • Cognitive deficit

(c) Predictors of compliance with PST
   • Educational level
   • Cognitive level
   • Score on post-training testing
   • Manual dexterity

(d) Attitudes and beliefs regarding AC (including concerns about AC, desire for self-care)

4. Economic analysis
   This will be based on a count of resources specific to AC. Included in this accounting will be:
   • medication, including warfarin, vitamin K, iron.
• laboratory tests, including INR, CBC.
• procedures, including upper endoscopy, colonoscopy.
• Blood product use, including packed red blood cells, fresh frozen plasma.
• Outpatient clinic use (scheduled and unscheduled), including ACS, physician, emergency room (record the primary reason for each visit, since PST may lead to greater empowerment which in turn may lead to a general increase in utilization of resources), telephone calls.
• Hospitalization, including length of stay, location (e.g., intensive care, ward), procedures, discharge diagnoses.
• Operation of ACS for each study arm.

D. Schedule Of Observations And Lab Tests

1. Assessments

   Scheduled assessments will be of the following types:
   a. Screening assessment: This will occur at the beginning of Part 1. Patients/caregivers will be evaluated for eligibility for Part 1 of the CSP Study, and information on medical history and medications will be obtained.
   b. PST training assessment: At the PST training visit (which occurs approximately one week after screening/baseline), patients/caregivers will be assessed for their initial competency in performing PST.
   c. PST competency assessment(s): Two weeks following PST training, the patient’s/caregiver’s competence with the INR monitor is evaluated. If the patient/caregiver is not competent after two weeks but the site personnel feel they may benefit from additional testing, the patient/caregiver may perform PST for two more weeks (total of four weeks) and then return to clinic for another assessment.
   d. Part 2 baseline assessment: Patients that pass Part 1 are eligible to participate in Part 2. At the Part 2 baseline visit, quality of life and AC satisfaction assessments are performed, and patients who meet Part 2
eligibility criteria are randomized to either HQACM or PST. Then, baseline clinical measures are obtained.

e. **Part 2 protocol follow-up visits and close-out assessment**: Follow-up visits for both HQACM and PST groups occur every 3 months after randomization. Patients who complete Part 2 will be followed for 2 to 4.75 years (8 to 19 follow-up visits). The close-out visit will coincide with the follow-up visit that takes place in the last three months of the patient's participation in Part 2. For a patient randomized to receive PST, these visits include assessment of the patient's/caregiver's performance and the performance of their monitors relative to the local point-of-care monitor and the laboratory monitor.

f. **Automated INR Follow-ups**: Patients/caregivers using PST will transmit INR values via automated telephone keypad input after each use of the home monitor. This occurs in Part 1 for all patients and in Part 2 for those assigned to PST.

g. **Part 1 and Part 2 Unscheduled Contacts**: There will be two types of unscheduled assessments:
   - assessment of telephone contacts
   - assessment of unscheduled visits.
Table 2: Part 1 Schedule of Assessments

Form 44, Conventional AC services information, filled once for each medical center at start of study
Form 45, Part 1 Training, filled once for each training session (not by Patient ID)

<table>
<thead>
<tr>
<th>Form (and number); Assessments/Procedures</th>
<th>Week</th>
<th>0</th>
<th>0-1*</th>
<th>2</th>
<th>4</th>
<th>Unsch contact</th>
</tr>
</thead>
<tbody>
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<td>Screening</td>
<td></td>
<td></td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Part 1 subject informed consent and HIPAA authorization</td>
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<tr>
<td>Part 1 caregiver informed consent and HIPAA authorization</td>
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</tr>
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<td></td>
<td></td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Part 1 entry criteria</td>
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<td>- Identify INR tester</td>
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<td></td>
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<tr>
<td>2: Patient demographics</td>
<td></td>
<td></td>
<td>X</td>
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<td></td>
</tr>
<tr>
<td>3: Part 1 medical hx, warfarin hx, medications</td>
<td></td>
<td></td>
<td>X</td>
<td></td>
<td></td>
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<tr>
<td>- AC duration</td>
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<td>- AC indication (AF, MHV)</td>
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<td>4: Unscheduled contact</td>
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<td>- AE’s reported</td>
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<tr>
<td>- Target INR range change</td>
<td></td>
<td></td>
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<tr>
<td>- If done, INR and/or CBC results</td>
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<td></td>
<td></td>
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<tr>
<td>- Weekly warfarin dose</td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>- Required for substudy sites only - If PST patient gets more cuvettes, download meter information and upload to website</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>5: Patient numeracy</td>
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<td>8: Patient dexterity</td>
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<td>X</td>
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<tr>
<td>9: DASS (AC satisfaction)</td>
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<td></td>
<td>X</td>
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<td>Week</td>
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<td>0-1*</td>
<td>2</td>
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<tr>
<td><strong>Form (and number); Assessments/Procedures</strong></td>
<td>Screening</td>
<td>Training competency #1</td>
<td>PST competency #2**</td>
<td>Unsch contact</td>
<td></td>
<td></td>
</tr>
<tr>
<td>10: Clinic training</td>
<td></td>
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<tr>
<td>- Dispense meter and supplies to subject</td>
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<tr>
<td>- Train on use of meter and supplies, phone system, and diaries</td>
<td></td>
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<tr>
<td>- INR tests in clinic by tester and by clinic</td>
<td></td>
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<tr>
<td>- If needed per wastage algorithm, do extra INR tests</td>
<td></td>
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<tr>
<td>- Change tester, if needed</td>
<td></td>
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<tr>
<td>- Hand out diaries</td>
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<tr>
<td>- Logon to website to set-up subject to report INR results by phone and enter target INR range</td>
<td></td>
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<tr>
<td>- If patient/caregiver dropped from study, take back meter and supplies, and clear memory, and clean meter</td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>Required for substudy sites: download meter and upload to website</td>
<td></td>
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</tr>
<tr>
<td>X May need to be filled separately by subject and caregiver</td>
<td></td>
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<tr>
<td><strong>Forms 11-15 filled when it is determined that subject cannot test on his/her own</strong></td>
<td></td>
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<tr>
<td>Week</td>
<td>0</td>
<td>0-1*</td>
<td>2</td>
<td>4</td>
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</tr>
<tr>
<td><strong>Form (and number): Assessments/Procedures</strong></td>
<td>Screening</td>
<td>Training competency #1</td>
<td>PST competency #2**</td>
<td>Unscheduled contact</td>
<td></td>
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<tr>
<td>16: PST assessment</td>
<td></td>
<td></td>
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<tr>
<td>- INR tests in clinic by tester and by clinic</td>
<td></td>
<td></td>
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<tr>
<td>- If needed per wastage algorithm, do extra INR tests</td>
<td></td>
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<tr>
<td>- Change tester, if needed</td>
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<td></td>
<td></td>
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<tr>
<td>- Collect filled diaries</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>- Required for substudy sites: download meter memory and upload to study website</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>- If needed, hand out new diaries and supplies</td>
<td></td>
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<td></td>
<td></td>
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<tr>
<td>- Clean meter</td>
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<td></td>
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<tr>
<td>- Clear meter memory if meter will be reassigned</td>
<td></td>
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<td></td>
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<tr>
<td>- Report AE’s</td>
<td></td>
<td></td>
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<tr>
<td>- At end of Part 1, take back meter and supplies, clean meter and clear memory. Required for substudy sites: download meter information and upload to website.</td>
<td></td>
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<tr>
<td>17: AE (one per AE)</td>
<td>If needed</td>
<td>If needed</td>
<td>If needed</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>18: Death</td>
<td>If needed</td>
<td>If needed</td>
<td>If needed</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>19: Stroke/TIA (one per event)</td>
<td>If needed</td>
<td>If needed</td>
<td>If needed</td>
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<td></td>
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<tr>
<td>20: Cardiac Event (one per event)</td>
<td>If needed</td>
<td>If needed</td>
<td>If needed</td>
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<tr>
<td>21: Bleeding (one per event)</td>
<td>If needed</td>
<td>If needed</td>
<td>If needed</td>
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<tr>
<td>22: PE/DVT (one per event)</td>
<td>If needed</td>
<td>If needed</td>
<td>If needed</td>
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<tr>
<td>23: Cellulitus (one per event)</td>
<td>If needed</td>
<td>If needed</td>
<td>If needed</td>
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<tr>
<td>24: Meter malfunction (one per event)</td>
<td>If needed</td>
<td>If needed</td>
<td>If needed</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>25: Other event (one per event)</td>
<td>If needed</td>
<td>If needed</td>
<td>If needed</td>
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<tr>
<td>26: SAE (one per SAE)</td>
<td>If needed</td>
<td>If needed</td>
<td>If needed</td>
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<td></td>
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<tr>
<td>27: SAE follow-up (one per SAE ongoing at prior visit/contact)</td>
<td>If needed</td>
<td>If needed</td>
<td>If needed</td>
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</tr>
</tbody>
</table>

* Training may occur at screening visit or up to one week later, individually or in a group  
** If subject/caregiver/team deemed not competent at week 2, they may be allowed to test for an additional 2 weeks  

PRIVILEGED AND CONFIDENTIAL: 5/18/2006; 33
Table 3: Part 2 Schedule of Assessments

<table>
<thead>
<tr>
<th>Month</th>
<th>0</th>
<th>3, 9, 15, 21, 27, 33, 39, 45, 51, 57*</th>
<th>6, 12, 18, 24, 30, 36, 42, 48, 54</th>
<th>Unscheduled contact</th>
<th>Same as last FU visit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Form (and number): Assessments/Procedures</td>
<td>Baseline FU</td>
<td>FU</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Part 2 subject informed consent</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Part 2 caregiver informed consent</td>
<td>When needed</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>28: Part 2 medical hx and medications</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Report CBC results</td>
<td></td>
<td></td>
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<tr>
<td>Report non-VA health care</td>
<td></td>
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<tr>
<td>Document warfarin status</td>
<td></td>
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<tr>
<td>4: Unscheduled contact</td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>- AE’s reported</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Target INR range change</td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>- Report INR and/or CBC results, if done</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>- Weekly warfarin dose</td>
<td></td>
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<tr>
<td>- Report if patient had a treatment assignment change</td>
<td></td>
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<tr>
<td>- Required for substudy sites only - If PST patient gets more cuvettes, download meter information and upload to website</td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>29 or 30: Health Utilities Index (HUI) for QOL</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>- Form 29 for subject self-assessment</td>
<td></td>
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<tr>
<td>- Form 30 for caregiver proxy assessment</td>
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<tr>
<td>9: DASS (AC satisfaction)</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
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</tr>
<tr>
<td>11: Caregiver demographics</td>
<td></td>
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<tr>
<td>12: Caregiver numeracy</td>
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<tr>
<td>13: Caregiver literacy</td>
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<tr>
<td>14: Caregiver mental status</td>
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<tr>
<td>15: Caregiver dexterity</td>
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</tbody>
</table>

11-15 filled when it is determined that subject cannot test on their own or complete the HUI on their own.

34; 5/18/2006
<table>
<thead>
<tr>
<th>Month</th>
<th>0</th>
<th>3, 9, 15, 21, 27, 33, 39, 45, 51, 57*</th>
<th>6, 12, 18, 24, 30, 36, 42, 48, 54</th>
<th>Same as last FU visit</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Baseline</td>
<td>FU</td>
<td>FU</td>
</tr>
</tbody>
</table>

### Form (and number); Assessments/Procedures

31: Part 2 entry criteria and randomization
- Part 2 entry criteria
- Identify INR tester
- Treatment assignment
- Hand out daily diaries
- Report target INR range change
- For HQACM, clinic INR test
- For PST:
  - Dispense meter and supplies to subject
  - INR tests in clinic by tester and by clinic
  - If needed per wastage algorithm, do extra INR tests
  - Change tester, if needed
  - Hand out home test diaries
  - Logon to website to enter subject's treatment assignment and change target INR range, if needed

|       |   |   | X |   |

32: Baseline information
- ECG, if none within 6 months of randomization

<p>|       |   | X |   |   |</p>
<table>
<thead>
<tr>
<th>Month</th>
<th>0</th>
<th>3, 9, 15, 21, 27, 33, 39, 45, 51, 57*</th>
<th>6, 12, 18, 24, 30, 36, 42, 48, 54</th>
<th>Same as last FU visit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Form (and number); Assessments/Procedures</td>
<td>Baseline</td>
<td>FU</td>
<td>FU</td>
<td>Unsch contact</td>
</tr>
<tr>
<td>33: Quarterly follow-up for PST</td>
<td></td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>- Report AE’s</td>
<td></td>
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<tr>
<td>- Report target INR range change</td>
<td></td>
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<tr>
<td>- Report treatment assignment change</td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>- INR tests in clinic by tester and by clinic</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>- If needed per wastage algorithm, do extra INR tests</td>
<td></td>
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<tr>
<td>- If PST patient now receiving HQACM, record INR results</td>
<td></td>
<td></td>
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<tr>
<td>- Dispense supplies and new diaries</td>
<td></td>
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<tr>
<td>- Collect filled diaries</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Required for Substudy sites: download data from meter and upload to study website</td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>- Clean meter</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Clear meter memory and collect meter and supplies if PST patient switched to HQACM or study participation ends</td>
<td></td>
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<tr>
<td>34: Quarterly follow-up for HQACM</td>
<td>X</td>
<td>X</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>- Report AE’s</td>
<td></td>
<td></td>
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<tr>
<td>- Report target INR range change</td>
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<tr>
<td>- Record INR’s from clinic tests</td>
<td></td>
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<tr>
<td>- Collect completed daily diaries</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>- Dispense new diaries</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>17: AE (one per AE)</td>
<td>If needed</td>
<td>If needed</td>
<td>If needed</td>
<td>If needed</td>
</tr>
<tr>
<td>18: Death</td>
<td>If needed</td>
<td>If needed</td>
<td>If needed</td>
<td>If needed</td>
</tr>
<tr>
<td>19: Stroke/TIA (one per event)</td>
<td>If needed</td>
<td>If needed</td>
<td>If needed</td>
<td>If needed</td>
</tr>
<tr>
<td>20: Cardiac Event (one per event)</td>
<td>If needed</td>
<td>If needed</td>
<td>If needed</td>
<td>If needed</td>
</tr>
<tr>
<td>21: Bleeding (one per event)</td>
<td>If needed</td>
<td>If needed</td>
<td>If needed</td>
<td>If needed</td>
</tr>
<tr>
<td>22: PE/DVT (one per event)</td>
<td>If needed</td>
<td>If needed</td>
<td>If needed</td>
<td>If needed</td>
</tr>
<tr>
<td>Month</td>
<td>0</td>
<td>3, 9, 15, 21, 27, 33, 39, 45, 51, 57*</td>
<td>6, 12, 18, 24, 30, 36, 42, 48, 54</td>
<td>Same as last FU visit</td>
</tr>
<tr>
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</tr>
<tr>
<td>Form (and number); Assessments/Procedures</td>
<td>Baseline *</td>
<td>FU</td>
<td>FU</td>
<td>Unsch contact</td>
</tr>
<tr>
<td>23: Cellulitis (one per event)</td>
<td>If needed</td>
<td>If needed</td>
<td>If needed</td>
<td>If needed</td>
</tr>
<tr>
<td>24: Meter malfunction (one per event)</td>
<td>If needed</td>
<td>If needed</td>
<td>If needed</td>
<td>If needed</td>
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<tr>
<td>25: Other event (one per event)</td>
<td>If needed</td>
<td>If needed</td>
<td>If needed</td>
<td>If needed</td>
</tr>
<tr>
<td>26: SAE (one per SAE)</td>
<td>If needed</td>
<td>If needed</td>
<td>If needed</td>
<td>If needed</td>
</tr>
<tr>
<td>27: SAE follow-up (one per SAE ongoing at prior visit/contact)</td>
<td>If needed</td>
<td>If needed</td>
<td>If needed</td>
<td>If needed</td>
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<tr>
<td>35: Non-VA Inpatient (one per inpatient stay)</td>
<td>If needed</td>
<td>If needed</td>
<td>If needed</td>
<td>If needed</td>
</tr>
<tr>
<td>36: Non-VA Outpatient care (one per outpatient visit)</td>
<td>If needed</td>
<td>If needed</td>
<td>If needed</td>
<td>If needed</td>
</tr>
<tr>
<td>37: Protocol Training</td>
<td>Fill for each training session on protocol for PST subjects</td>
<td></td>
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<tr>
<td>38: Missed Visit</td>
<td>Completed each time a patient in either group misses a scheduled follow up visit</td>
<td></td>
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<tr>
<td>39: Completion Termination</td>
<td>When subject completes or terminates study participation</td>
<td></td>
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</tr>
</tbody>
</table>

* Baseline may occur at same visit as Part 1 verification of competency
** Closeout visit includes same assessments and procedures as 6 month FU visit
2. **Visit details**

Part 1 includes 3-4 contacts: the Screening Visit, the PST Training Visit, and the Competency Assessment (maximum of 2 visits). Part 2 includes baseline and 8-19 Protocol Follow-up Visits (the last of which is the close-out visit). In addition, unscheduled telephone calls or visits may occur in either Part 1 or 2 at the discretion of the ACS Manager.

**a). Part 1 Screening Visit:** For patients who meet the Part 1 entry criteria, the SC will then collect demographic information and data on the subject’s medical, warfarin, and medication history.

Patients who participate in Part 1 that are deemed ineligible for Part 2 (e.g., because they did not pass the competency assessment) may be re-screened for the study at the discretion of the site staff.

**b). Part 1 Training Visit:** Each subject/caregiver in Part 1 will undergo a training program on PST principles (including correct use of the ProTime® meter), use of the phone system to report results of PST tests, and how to fill out two diaries: a daily diary to record daily dose of warfarin, and any adverse events or medical care received; and a home testing diary to record INR and other results from PST. This visit may occur on the same day as screening or up to one week after screening.

At the training visit, the SC will train the subject/caregiver on maintaining standardized home monitoring diaries, and assess the subject on numeracy, literacy, mental status, dexterity, and satisfaction with AC treatment.

In addition (see Form 10), the SC will provide the tester (subject/caregiver) with a meter and cuvettes/lancets so they can do practice tests. Once the SC feels the tester is performing adequately, the SC will do a test on the subject using the clinic’s meter and supplies and compare the results to those from the tester using their own meter and supplies. If the results meet the criteria of the competency and wastage algorithm, the tester is deemed trained and the SC ensures the tester is sent home with enough supplies to do PST twice a week for two weeks. Otherwise, additional tests are done to
help determine the reason for the discrepancy (e.g., tester error, faulty tester meter, or faulty tester supplies). If the meter or supplies are the problem, the SC will give the tester replacements.

If the tester is at fault, the response of the SC will depend on the particular circumstances of each case.

1. Drop the subject from the study if the tester was a subject who has no caregiver to provide assistance.
2. Change the tester to the (new) caregiver and repeat the training if the deficient tester was a subject who has a caregiver or the tester was a caregiver but the subject has another caregiver who can provide support.

The SC will also train the subject/caregiver on the proper use of the phone system for reporting results from INR tests performed at home.

If at the end of this visit the subject/caregiver are deemed sufficiently trained to perform the protocol, the SC gives them 2 blank "daily diary" sheets, 2 blank "home testing diary" sheets, and a folder in which the subject should keep all documents related to performing PST and reporting results. The SC will also instruct the subject/caregiver to do PST twice a week for the next two weeks and give them cuvettes and lancets for the testing.

If, in the opinion of the SC and the SI, the subject’s/caregiver’s response to training indicates they are incapable of performing the protocol, the subject/caregiver must be dropped from the study.

c). Part 1 PST Competency Assessment Visit(s): The process to assess PST competency will take either 2 weeks (one visit) or 4 weeks (2 visits) depending on whether the subject/caregiver tester displays competency after two weeks of performing PST (see the criteria on the Patient Self-Testing Assessment form). At each competency assessment visit, the SC will:

- download information from the meter (required for substudy sites only);
- collect the diaries for the prior study period (and, if 4 weeks of training is needed, provide new diaries and additional cuvettes and lancets as needed);
- test the subject/caregiver for competency. The competency assessment involves the same testing procedures done at the training visit by the tester (subject/caregiver) and SC using the two sets (tester's and clinic's) of meters and supplies and the competency and wastage algorithm;
- If needed, fill the adverse events (AE) form (one form per AE reported), the forms to gather more information about specific AE's which occurred, the Serious Adverse Event (SAE) form (one form per SAE reported), and the SAE follow-up form.

If, after a reasonable effort, the SI and SC conclude that the subject/caregiver is unable to demonstrate competency in any level of PST (i.e., they are unable to use the meter correctly), the SI and SC may deem the subject ineligible for Part 2 of the study (in which case their care will revert to their usual AC care). This determination may occur at either the two week or four week competency visit.

On the other hand, if the SI and SC conclude at the two week assessment that the subject/caregiver will benefit from two more weeks of testing, they may continue in Part 1 though the tester will need to be changed.

d). Part 1 Unscheduled Visits/Contacts: Unscheduled telephone contacts or clinic visits (see Form 4) may occur at the discretion of the SC. Reasons for an unscheduled contact/visit include the reporting of out-of-range INR values, abnormal lab values, or potential significant events, failure to follow the protocol schedule, and the need for additional cuvettes or lancets.

At an unscheduled contact in Part 1, the SC will document any change in the subject’s target INR range, the subject’s warfarin dose, and the results of any INR test or CBC performed.
If needed, the SC or SI will also fill the adverse events (AE) form, forms to gather more information about specific AE’s that occurred, the SAE form, and the SAE follow-up form. If deemed necessary, an INR test and/or a CBC may be performed.

e). Part 2 Baseline Evaluation and Randomization: The baseline visit must take place within 30 days of the Part 1 visit during which the subject was determined to be competent in performing PST.

1. Informed Consent: Each subject/caregiver who shows PST competency in Part 1 will be asked to provide their consent to participate in Part 2, the randomized clinical trial portion of CSP #481.

2. Assessments and Procedures: After obtaining informed consent from the subject/caregiver, the SC gathers information about the subject’s medical history, warfarin history, and medications since the Part 1 screening visit. The subject/caregiver will then complete the Health Utilities Index (HUI) quality of life instrument and the Duke Anticoagulation Satisfaction Scale (DASS).

The subject will also have a CBC done to provide a reference measure for comparison with the values obtained later in the study (at the SI’s discretion, the subject may have a CBC performed at the quarterly follow-up visits and unscheduled contacts in Part 2). After review by the SC, retain all clinical information in the Subject Medical Record (study clinic chart).

If needed, the SC or SI will also fill the adverse events (AE) form and, forms to gather more information about specific AE’s that occurred, the SAE form, and the SAE follow-up form.

The SC then determines if the subject/caregiver meet the entry criteria listed on the Part 2 Entry Criteria and Randomization form. Those who do are eligible for randomization to either HQACM or PST.

After randomization, the SC will collect personal, medical and medication information on the subject (see Form 28). If results are available from an ECG on the subject that took place within six months of randomization, the SC will provide that information to the CSPCC. Otherwise, an ECG will be done on the subject and the results will be sent to the CSPCC. The ECG results will be used as a pre-event
measure to help assess if the subject has had a myocardial infarction (MI) later in the study.

If the subject is assigned to PST treatment, the SC will give the subject a sufficient number of blank copies of the "home test diary" to cover the period until the 3 month follow-up (10 copies for PST twice a week; 5 copies for PST once a week; and 2 copies for PST once every four weeks). In addition, if the patient does not yet have a meter, the SC will provide a meter and related supplies.

f). Part 2 Protocol Follow-up Visits: The target dates for the subject's/caregiver's in-person follow-up visits with the site staff are every three months after randomization. Each visit should occur no earlier than two weeks before and no later than two weeks after the target date.

At each visit, the SC will:

- gather data on medical and warfarin history and medications, any AE's, SAE's, or study endpoint events since the last clinic visit, and follow-up on any SAE's ongoing from prior study visits;
- review treatment objectives and answer questions;
- obtain clinical and resource-use measures;
- determine if the subject has received any non-VA medical care
- collect completed "daily diary" sheets and give the patient/caregiver 15 blank sheets to cover the period until the next quarterly visit;
- if ordered by the SI, get a CBC done on the subject;
- record the average weekly warfarin dose or indicate that the patient has been taken off of warfarin permanently
• determine if there was a change in target INR range. If a change was made, the SC documents this on the appropriate case report form (follow-up form for PST or the one for HQACM).
• for PST subjects only:
  - review self-testing procedures with the subject;
  - count the number of cuvettes brought in by the subject (separately, the total number and the number passed the expiration date);
  - perform a comparison test between the subject’s and the point-of-care clinic’s meter and, if the results are discordant, perform additional tests following the competency/wastage algorithm;
  - document any treatment assignment change;
  - collect completed “home testing diaries” for the prior period and give the subject/caregiver a sufficient number of blank copies to cover the period until the next follow-up visit (10 copies for PST twice a week; 5 copies for PST once a week; and 2 copies for PST once every four weeks);
  - download information from the meter (required for substudy sites only); and
  - give the subject/caregiver additional testing supplies and record the number of cuvettes dispensed.
• for HQACM subjects only, record the results of the monthly INR tests performed by the clinic since the prior quarterly visit.

Also, every six months after randomization, the subject/caregiver will fill the HUI and DASS forms.

Subjects/caregivers who are identified as having significant abnormalities in laboratory values (based on local reference ranges) or who report adverse experiences or AE’s (especially a serious adverse experience or SAE) will be referred to the SC to coordinate follow-up, together with the subject’s physician as appropriate. All subjects/caregivers will be told of their INR during the visit and will be asked how they would respond to this result if they were to make their own dosing decisions.
g). Study Closeout Visit: At the end of the subject's participation in the study, a subject assigned to PST must return the INR monitoring meter and any unused supplies. In addition, since study follow-up visits to the clinic are scheduled to occur every three months after randomization, it is likely that the final scheduled visit for many study participants will not take place in the last month of the study. To avoid the need for a PST subject to visit the clinic after his/her last quarterly study visit simply to return the meter and supplies, the final quarterly visit will also serve as the subject's closeout visit. Since the study's end date is May 31, 2008, the subject closeout visit will take place during the final 3 months between March 1 and May 31, 2008. Therefore, not all subjects would be followed until May 31; the closeout visit for a given subject would correspond to his/her final quarterly follow-up visit.

The closeout visit includes all procedures and assessments done at the six-month post-randomization visit, including the HUI and DASS. In addition, the Completion/Termination form (Form 39) must be filled to document the end of the subject's participation in the study.

h). Part 2 Unscheduled Telephone Calls/Visits: In addition to the monthly clinic visits for subjects/caregivers in the HQACM group and Protocol Follow-up Visits for all subjects/caregivers, the subject/caregiver may have unscheduled telephone calls/visits by the SC based on information obtained as part of any study assessment and the judgment of the SC. Reasons include out-of-range INR values, specific abnormal laboratory values, potential AEs/SAEs, or the need for additional supplies. The SC will record such visits (including the reason for the visit and the disposition) on a Form 4 ("Unscheduled Contact Report").

The SC will also:
- Determine if the subject had any AE's since the last study visit or contact (and, if so, fill out the appropriate forms to report the AE’s, SAE’s or study endpoints);
- Follow-up on any SAE's ongoing from the last visit or contact;
- Determine if there was a change in target INR range;
- If the SI orders a CBC or INR test, record the results on Form 4; and
• Enter the subject’s average weekly warfarin dose or indicate that the subject has discontinued warfarin treatment permanently.

E. Care Of Patients After The Study

Once a patient’s completes study participation, his/her VA treating physician will provide medical care. The study has no provisions for treatment beyond this point. Study data regarding outcome will be shared with the VA treating physician.

IV. BIOSTATISTICAL ISSUES

A. Primary Hypothesis

For the primary objective, we want to test the null hypothesis that the survival curves for the HQACM and PST groups are the same by comparing their hazards, given a one year enrollment period and a minimum of two years of follow-up. For clarity, we will express this comparison in terms of the hazards that result from annual event rates of \( p_c \) (c for “control”) for subjects receiving HQACM care at 4-week testing intervals and \( p_i \) (i for “intervention”) for subjects performing PST at 1-week testing intervals; that is, \( H_0: p_c = p_i \) versus \( H_1: p_c \neq p_i \).

B. Sample Size Issues

1. Estimation of Event Rates

To estimate the annual event rate as defined for CSP #481 (strokes, major bleeds, or death) for the HQACM (control) group, we looked at those reported in the literature for trials of oral anticoagulation.

Note that there are two significant caveats to this data:

a. It is not always clear as to when fatal strokes and fatal bleeds are included in the death rates; therefore the potential for some degree of “double counting” for these events exists.

b. When possible, we have extracted "on treatment" data as this is most applicable to CSP #481 since we have no placebo therapy arm and all patients will be...
on drug. However, not all studies reported "on treatment" / efficacy data, and in some cases it is unclear as to which was reported.

The following table summarizes these results, including those from six studies of patients with AF, two of patients with heart valves, and two of patients with deep venous thrombosis (DVT).

The six studies of AF include CAFA (Canadian Atrial Fibrillation Trial, Connoly et al. 1991), SPINAF (VA Cooperative Study #308, Stroke Prevention in Atrial Fibrillation, Ezekowitz et al. 1992), BAATAF (Boston Area Anticoagulation Trial in Atrial Fibrillation, BAATAF Investigators 1990), SPAF I (Stroke Prevention in Atrial Fibrillation – NIH, SPAF Investigators 1991), AFI (Atrial Fibrillation Investigators who pooled data from 5 trials, including the four listed above as well as AFASAK (Scandinavian) with a total of 1,889 patient-years, AFI 1994), and EAFT (European Atrial Fibrillation Trial of secondary prevention with 507 patient years, EAFT Study Group 1993).

The studies of heart valve patients include the Dutch Registry (6,475 patient-years, Cannegeiter et al. 1995) and a presented but unpublished study, ESCAT I (European Self Control of Anticoagulation Therapy), which is similar in intent to CSP #481 (over 2,300 patient-years; routine anticoagulation management versus PST/PSM with target INR range of 2.5 to 4.5).

The two DVT studies are of interest in terms of total complication rate as well as beneficial effect on total mortality in excess of that explainable by recognized hemorrhage or TE. These studies are by Kearon et al. 1999 (first episode of DVT) and Schulman et al. 1997 (412 patient years, second DVT).
Table 4: Event Rates in Trials of Oral Anticoagulation

<table>
<thead>
<tr>
<th>Study</th>
<th>Stroke</th>
<th>Major Bleed</th>
<th>Death</th>
<th>TOTAL</th>
</tr>
</thead>
<tbody>
<tr>
<td>AF trials</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- CAFA</td>
<td>2.1</td>
<td>2.5</td>
<td>3.7</td>
<td>8.3</td>
</tr>
<tr>
<td>- SPINAF</td>
<td>0.9</td>
<td>1.3</td>
<td>3.3</td>
<td>5.5</td>
</tr>
<tr>
<td>- BAATAF</td>
<td>0.4</td>
<td>0.4</td>
<td>2.3</td>
<td>3.1</td>
</tr>
<tr>
<td>- SPAF I</td>
<td>2.3</td>
<td>1.5</td>
<td>2.2</td>
<td>6.0</td>
</tr>
<tr>
<td>- AFI</td>
<td>1.4</td>
<td>1.3</td>
<td>3.6</td>
<td>6.3</td>
</tr>
<tr>
<td>- EAFT</td>
<td>4.0</td>
<td>2.8</td>
<td>8.0</td>
<td>14.8</td>
</tr>
<tr>
<td>Heart value trials</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Cannegether</td>
<td>0.7</td>
<td>2.7</td>
<td>2.9</td>
<td>7.3</td>
</tr>
<tr>
<td>- ESCAT I</td>
<td>Only counts of events presented</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DVT trials</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Kearon</td>
<td>1.3</td>
<td>3.8</td>
<td>1.2</td>
<td>6.3</td>
</tr>
<tr>
<td>- Schulman</td>
<td>0.7</td>
<td>2.4</td>
<td>2.4</td>
<td>5.5</td>
</tr>
</tbody>
</table>

Based on these results, we will be conservative and assume a 5.5% (= p_c) annual event rate for the HQACM group. We will also consider 1.75% to be the minimum clinically significant decrease in annual event rate (p_i = 3.75%) due to the PST intervention.

2. Power Calculation

Power calculations are developed in detail for the percent of patients that experience an event (TE, major bleed, or death by any cause). Although patient randomization will be stratified, the stratification was not reflected in the sample size calculations (but will be accounted for in the analysis).

Assume the following:
1. Minimum length of follow-up: 2 years
2. Length of patient accrual: 1 year

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3. Statistical power level: .90
4. % noncompliance in the control group (those who “drop-in” to the intervention): 0 since they will not have access to self-monitoring equipment.
5. % noncompliance in the intervention group (“non-adherers” whose actual treatment is essentially the control): 10%.
6. 1-year % of control patients that will have an event during the follow-up period: 5.5%.
7. % relative reduction in control rate due to the intervention: 31.8%, or a drop from 5.5% in the control group to 3.75% due to the intervention.
8. 2-sided significance test at .05.
9. the data will be analyzed based on the intent to treat principle whereby each patient is included in the group to which he/she is randomized.

The sample size is based on the logrank test [Freedman, 1982] for time to first event. The following power curves obtained from using Frank Harrell’s CPOWER program [Harrell, 1999] show the sensitivity of the power level to changes in assumptions 5-7 listed above. CPOWER assumes exponential distributions for both arms and uses the methods of George and Desu [1993] and Lachin and Foulkes [1986].

The following page shows power curves for a total sample size of 3134 which is required based on the assumptions listed above. There are 4 plots: one each for noncompliance in the intervention group of 0, 5, 10, and 15%. For a given plot, the x-axis shows the 1-year % of control patients with an event, and there is a curve for 4 different levels of relative reduction in event rate (25, 31.8, 35, and 40%) resulting from the intervention in each graph.

The bottom curve in the lower left plot shows that n=3134 would provide power of about .71 if the actual relative reduction is 25% instead of 31.8%. The next to bottom curve in the lower right plot shows that an increase in the non-adherence rate for the intervention from 10% to 15% would decrease the power to about .87.

**Based on these calculations, we will set the sample size at 3200. We expect each site to enroll 100 patients, so a total of 32 sites will be required.**
Power curve graphs (1 page) go here
C. Statistical Analysis Plans

1. Method of Randomization. Randomization will be stratified, with the strata defined in Table 1 (i.e., by site, duration of AC, and indication for AC). The actual mechanics of the randomization will be determined by the Palo Alto CSPCC.

2. Proposed Analyses

(a). Primary Efficacy Variable

Clinical event rates, analyzed separately, will include stroke, major bleeds, and mortality. Operational definitions of the clinical events of interest are listed in Table 5.

Table 5: Operational Definitions of Clinical Events for THINRS Study

<table>
<thead>
<tr>
<th>CLINICAL EVENT</th>
<th>DEFINITION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thromboembolism</td>
<td></td>
</tr>
<tr>
<td>• Stroke – primary outcome</td>
<td>Loss of brain function persisting more than 24 hours attributed to cerebral ischemia, localized to a portion of the brain supplied by one vascular system for which no other cause can be found on brain imaging studies. Major stroke is defined by a Rankin score of 4 or 5.</td>
</tr>
<tr>
<td>• Other TEs - secondary outcome</td>
<td></td>
</tr>
<tr>
<td>– DVT</td>
<td>Swelling pain, and/or tenderness of the extremity with abnormal impedance plethysmography, Doppler ultrasound, or venography.</td>
</tr>
</tbody>
</table>
| – PE                 | In the setting of clinical suspicion for PE, either of the criteria below are present:  
  1. A ventilation-perfusion scan demonstrates high probability (per PIOPED definition, Stein et al. 1995, Gray and Bessent 1998); OR  
  2. Pulmonary angiography is diagnostic (reveals intraluminal defect(s) or abrupt cutoff of a vessel); OR  
  3. CT scan or MRI is positive for intraluminal clot; OR  
  4. The lung imaging study is non-diagnostic for PE but there is objectively diagnosed (compression ultrasound, venography, or MRI) deep venous thrombosis; OR  
  5. Autopsy.                                                                 |
| – Other visceral infarctions | Tissue necrosis in internal organs following cessation of blood supply, as detected by arteriogram.                              |
### Bleeding Events

<table>
<thead>
<tr>
<th>Clinical Event</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major bleed (for THINRS trial) - primary outcome</td>
<td>Severe: Retroperitoneal, intracranial, intraspinal, intra-ocular, or pericardial bleeding or any other source of bleeding that results in hemodynamic compromise. Moderate: Bleeding requiring transfusion of red blood cells or whole blood but does not result in hemodynamic compromise or bleeding associated with a drop in hemoglobin of ≥ 2g/dL (or hematocrit ≥15%) from baseline.</td>
</tr>
<tr>
<td>Minor bleed (for THINRS trial) - secondary outcome</td>
<td>Minor: Bleeding that does not require transfusion or cause hemodynamic compromise but alters the normal care or progress of the patient. Incidental bleeding: Bleeding that does not require transfusion or cause hemodynamic compromise. It also does not alter the normal care or progress of the patient.</td>
</tr>
</tbody>
</table>

### Other Events

<table>
<thead>
<tr>
<th>Clinical Event</th>
<th>Definition</th>
</tr>
</thead>
</table>
| Myocardial infarction - secondary outcome | An endpoint MI (acute, evolving, or recent MI) is defined by:  
1. Enzyme or ECG evidence:  
   - elevation of CK-MB >ULN or, total CK >ULN (if no CK-MB values are available), or  
   - new, significant (*0.04 s) Q waves in *2 contiguous leads.  
2. For subjects who under-go revascularization, an endpoint MI is defined as follows:  
   - Peri-PCI: CK-MB (or total CK, if CK-MB is unavailable) *3 times the ULN and increased by at least 50% from level before the procedure  
   - Peri-bypass: CK-MB (or total CK, if CK-MB is unavailable) *5 times the ULN and increased by at least 50% from level before the procedure  
   - Any revascularization: New, significant (*0.04 s) Q waves in 2 contiguous ECG leads  
3. Cardiac troponin (I or T) often are used to diagnose MI and are part of the definition proposed in the ESC/ACC Consensus Statement. Because troponins may remain elevated for 7-14 days and because the magnitude of troponin elevation has an uncertain relationship with outcomes, the use of troponin in an endpoint has limitations. The protocol mandates CK and CK-MB collection in subjects with suspected reinfarction and after PCI and CABG. There may be subjects who have a suspected reinfarction without available CK/CK-MB data but with troponin data. For these subjects, an MI may be adjudicated by the Clinical Events Classification Group (CEC) when there is a preponderance of clinical evidence based on signs, symptoms, ECG changes, and troponin data. If troponin data are used, the value must be *2*ULN.  
4. Pathologic evidence of an acute MI. |
Figure 5 provides an algorithm to classify a surgical bleeding incident (major bleed, minor bleed, or not an event).

**Figure 5: Algorithm For Surgical Bleeding**

If the patient had a surgical procedure, and was transfused with blood,

- Note the number of units of blood transfused during the intra-operative period
- Determine if the bleeding was excessive ("excessive bleeding" would be any number of transfusions that were beyond the number specified in the OR schedule sent to the blood bank prior to the surgery)
  - YES: Consider as a Major bleeding event
  - NO: Not an event

- Note the number of units of blood transfused in the post-operative period
- Adjudicate to the operating physician to determine if transfusion was unexpected
  - YES: Is it a Major bleed (by our definition)
    - YES: Consider as a Major bleeding event
    - NO: Not an event
  - NO: Not an event
(b). Secondary Efficacy Variables

TTR will be defined using the method of Rosendaal (1993); that is, the INR for each day is defined by linearly interpolating from observed values, and TTR is defined as the percentage of such patient-days which are within target range. TTR will be measured both with and without adjustment for event risk.

A loss function will be defined by integrating the observed INRs over the distribution of outcomes per INR value. The loss function is derived from published data from Cannegeiter (1995) fitted to logistic models for TE and bleed (Samsa, 2000). Specifically, if \( p \) is the annual probability of an event, the fitted model for TE is \( \text{logit}(p) = -0.7251 - 1.1723 \text{INR} \), and the fitted model for bleed is \( \text{logit}(p) = -8.8426 + 0.8291 \text{INR} \).

Other events include “non-stroke” TE, and minor bleeds (Table 5).

Competence and compliance with PST (for the PST group only). Competency will be assessed by concordance between concurrent patient and provider INR results. Compliance will be assessed based on strip counts, meter memory and automated INR follow-up log relative to expected results.

Satisfaction with care will be quantified using the Duke Anticoagulation Satisfaction Scale (DASS). Each subject will be asked, both before and after the follow-up period, whether he/she prefers one management strategy over the other.

AC-related QOL will be quantified using the Health Utilities Index (HUI).

The cost effectiveness will be based upon an incremental cost-effectiveness ratio (ICER). The denominator will be based upon differences in event rates (in turn derived from differences in TTR). The numerator will be based upon differences in costs (i.e., based upon both observed utilization and putative differences in event rates derived from differences in INRs). Cost-effectiveness analysis will not explicitly consider QOL.

To access ability to make a dosing decision, the patient/caregiver will be told of the INR during the clinic visit and asked how they would respond to this result if they were to make their own dosing decisions.

3. Methods of Analysis

Baseline Comparability. Because of the size of this study, we expect the randomization process to balance baseline characteristics and produce comparable groups of patients. Baseline comparability between treatment
groups will be evaluated with respect to entry criteria, as well as demographic, physical and laboratory characteristics. We will use summary statistics and graphical techniques, such as boxplots, to compare the baseline characteristics of treatment groups.

**Effect of the Intervention:** The primary objective is to assess the effects of PST vs. HQACM on the incidence of events. To do this, the time from randomization to first event or to the end of the study will be analyzed as the primary endpoint using the stratified logrank test described above. Cumulative survival curves will be constructed by the Kaplan-Meier methods. The Cox life table regression method will be used to calculate estimates of relative risk, provided the model fits the data. We will use Harrell’s “Hmisc” and “Design” S-Plus libraries [Harrell, 1996] to assess model fit and produce diagnostic graphics.

Compliance analyses: Subject compliance will be measured by:
- percentage of tests performed within two days of the scheduled date, and
- Concordance of patient reports and meter memory download (substudy sites only).

**Safety, Adverse Experiences:** these will be tabulated by treatment arm and study site. In addition to tabulating the incidences, safety endpoints will also be analyzed by the time to first event analysis using the Cox proportional hazards regression model.

**D. Interim Analysis**

Once ongoing, this study will be monitored by the Data and Safety Monitoring Board (DSMB), an independent outside group which periodically reviews the accumulating results to assess treatment efficacy and to decide on early termination of the study. The DSMB will receive semi-annual interim reports from the CSPCC and will meet annually, in a joint meeting with the Palo Alto CSPCC Human Rights Committee.

Performing repeated significance testing on accumulating outcome data as part of a "stopping rule" may inflate the overall type I error rate. This statistical problem has
been discussed extensively in the statistical literature during the past twenty years, and various approaches to address this issue have been proposed. The DSMB will develop the guidelines it will follow in deciding on early termination of the study at its initial meeting, and these guidelines should address the issue of interim analyses.

E. Analysis Of Utilization and Cost Data

1. Overview

The methods for this study build on those that we have successfully used for previous Cooperative Studies. There are changes to the methods based on lessons learned from these earlier studies and to take advantage of new additions to VA data systems. While the methods described below and in Section XVI may appear complex because there are so many different sources of data, the approach is straightforward; capture utilization data as efficiently as possible and then apply standardized costs to the measure of utilization. In collecting the VA utilization data, we will use data from centralized VA databases wherever possible. Because not all VA data are available from the centralized VA data in Austin, however, it may be necessary to collect some information from the local data systems at each study site. Non-VA utilization data will be obtained through patient diaries and hospital record review. This study will also draw on the recent work by the VA Health Economics Resource Center (HERC) to facilitate cost analyses in the VA. Methods may be adjusted as HERC develops new estimates of the costs of VA care.

The VA does not regularly produce patient-specific cost data. Thus, VA costs must be estimated. HERC has estimated costs for each VA health care encounter. The VA Decision Support System (DSS) national data extracts also have estimates of VA costs, including the costs of types of services that are not present in the HERC data such as outpatient pharmacy use. To make the results applicable for the whole country, we have decided to use nationally representative costs instead of the costs at each facility. This also facilitates the integration of non-VA costs with VA costs. The DSS cost data are based on local, not national costs. Thus, the DSS cost estimates will be adjusted to national averages.
In estimating the costs of care, we will assume that it is unlikely that this study will have any effect on the care provided to patients when they do seek care for a specified condition beyond variation in length of stay for inpatient care and variation in procedures or medications for ambulatory care. Thus, we will use standardized estimates, adjusted for length of stay, based on Diagnostic Related Groups (DRGs) for acute inpatient care and per diem costs for all other inpatient care, including long term care. Similarly, we will use standardized estimates CPT-4 codes to assign costs for ambulatory care.

Given that the experience of previous cooperative studies (and most non-VA studies) has been that hospital costs dominate the costs of care, we will spend a disproportionate amount of effort trying to capture information on these less common, but expensive events. While information on the patient’s use of VA hospitals is available from centralized VA data, there is no centralized source for non-VA care. Thus, extra effort is budgeted to track the utilization of non-VA hospitals. Specifically, we will regularly query patients about their non-VA hospital use, and then have the SC’s request discharge abstracts or go to each hospital to abstract the required information. The study consent form specifically states that this will be done. Conversely, the information we collect about non-VA outpatient encounters will be limited to that reported by the patient.

The costs for this study will be measured from the perspective of all health care costs. Reporting the results from this perspective (instead of VA costs alone) will make the findings useful to a broader audience. Since this is a VA study, we will also consider the VA cost perspective.
2. Cost-Effectiveness Analysis

The main hypothesis of the investigators is that home-based PT-INR monitoring will reduce adverse event rates (i.e. improve patient outcomes). The cost-effectiveness of this intervention is a secondary outcome of the study. As noted above, the effectiveness analysis will be based on the incremental cost-effectiveness ratio. The purpose of the rest of this section is to use secondary data to provide a description of the current costs of care for study patients and to make a preliminary estimate of the cost-effectiveness, given the assumed study effects.

While it is not possible to exactly replicate the study eligibility criteria from VA secondary data, the VA outpatient data do identify the clinics at which patients are treated and include International Classification of Diseases (ICD) codes. We used these data to identify all patients who used the warfarin clinic at least once in FY 1998. Among these patients, we used ICD codes to identify those with a heart valve replacement, or with atrial fibrillation and at least one of the following conditions (age >65, hypertension, stroke, diabetes, or congestive heart failure). For the patients meeting these criteria, we pulled data for all VA utilization for one year after their first use of the warfarin clinic in FY 1998.

In FY 1998 there were 12,827 patients who meet the above criteria. Of these, 3,471 were identified as valve patients and 9,356 as atrial fibrillation patients (140 were in both groups). These patients are high risk patients; 836 (6.5%) died in the 1-year follow up window, and 1,629 (12.7%) had died as of a check of VA centralized records in early February 2000. The other event rates that could be easily identified from ICD codes for the one-year follow-up period were stroke and pulmonary embolism. (It is more difficult using the VA files to identify occurrences of the other event types for this study, namely DVT, other visceral infarctions, and warfarin related hemorrhage including those that required a transfusion as part of an inpatient hospitalization. We hope to have these estimates available to present at the CSEC meeting). In this sample, event rates for stroke and PE were 1 and 0%, respectively. Thus, this sample of VA patients produced an estimated event rate of at least 7.5% which is higher than the 5.5% event rate used for the power calculations. For the preliminary cost-
effectiveness calculations below we will use the 5.5% event rate. We must reiterate that ICD code based patient selection criteria do not exactly replicate those that will be used by the proposed study. The same caveat applies to the identification of events and not all events could be included. We have no way of knowing how the actual study selection criteria will effect the numbers reported here.

The $7,200 average cost these patients incurred is higher than that of the average VA patient. The table shows the average costs (using 1998 Medicare reimbursement rules) for likely study patients by type of care (outpatient, inpatient, and long term care). These cost estimates do not include the costs of any outpatient pharmacy or laboratory utilization as these data are not included in the VA’s centralized data system. The sum of these reported costs is over $91,000,000.

<table>
<thead>
<tr>
<th>Care Category</th>
<th>Number of Patients Receiving Care</th>
<th>Cost per Patient Receiving Care</th>
</tr>
</thead>
<tbody>
<tr>
<td>Outpatient</td>
<td>12,687</td>
<td>$1700</td>
</tr>
<tr>
<td>Inpatient</td>
<td>3679</td>
<td>$17,600</td>
</tr>
<tr>
<td>Long-term care</td>
<td>355</td>
<td>$15,800</td>
</tr>
<tr>
<td><strong>TOTAL</strong></td>
<td><strong>12,687</strong></td>
<td><strong>$7,200</strong></td>
</tr>
</tbody>
</table>

To conduct a preliminary cost-effectiveness analysis, we used the intervention costs used in the study budget, $750 for the monitor and $950 per PST patient for cuvettes in Part 2 of the study, for a per patient cost of $1700 in the two-year follow up period. This estimate will not include the other costs of home monitoring (patient training and patient phone contact with clinic staff) or the savings to the VA of reduced visits to the AC clinic (staff time and lab testing). This yields a conservative estimate of the costs of the intervention since the savings from reduced clinic visits are almost certainly greater than the added clinic costs associated with home monitoring.

We used the VA data to estimate the cost of the adverse events. These were obtained from the VA data for the patients identified as possibly being eligible for this
study. The mean cost of those events we could identify was $16,300. Note that these cost estimates are for inpatient care only, and do not include the rehabilitation or skilled nursing costs that stroke patients frequently incur.

For the 1600 PST patients in the study, assume the costs of monitors and cuvettes will be $2.72 million. Reducing the 5.5% annual event rate to 3.75% yields 70 events prevented during the two years of follow-up. The associated reduced hospital cost would be $1.14 million. Thus, the net incremental cost of doing the trial would be $1.58 million or $22,600 per event prevented.

This estimate is sensitive to the assumptions that we have made. All of the changes listed below are in reference to the base case described above.

If we decrease the $1.58 million figure by the cost savings from reduced testing at the medical center (16 scheduled visits to the AC clinic are eliminated for each PST patient at $30 per visit) the incremental costs are $811,000 or $11,600 per event prevented.

Doubling the cost of hospitalization reduces the net cost from $2.72 million to $438,000 or $6300 per event prevented. We did not do a sensitivity analysis for reducing hospital costs as this did not seem plausible, given the type of events being considered.

An event rate decrease due to the intervention of 2% instead of 1.75% (due either to greater effectiveness or a higher event rate) would prevent 80 events and reduce the net cost to $1.42 million or $17,700 per event prevented. Conversely, if the change in event rates is only a 1% decrease, the number of events prevented falls to 40. The resulting net cost is $2.07 million or $51,700 per event prevented. The incremental cost effectiveness ratio is especially sensitive to changes in the event rate because this changes both the numerator and the denominator.
V. DATA COLLECTION AND MANAGEMENT

After the study is approved, data forms will be field tested. An Operations Manual will be provided to the investigators as a guide to the operation and management of the study as well as a technical reference manual. A training session at the kickoff meeting is planned prior to the initiation of patient enrollment for all study participants to assure uniformity in patient management and data collection procedures, and to train the participants in study procedures.

The SC at each medical center will assemble the completed data forms on a daily basis and fax the forms to the CSPCC. The original forms will be kept at the SI's (SI's) office.

DataFax software (Clinical DataFax Systems, Inc.) will be used for data collection and editing. With DataFax, forms completed at the study sites are faxed to the CSPCC where the data images are delivered directly into a SUN server which stores the images as fax files and uses an optical character recognition paradigm to process and store the information into the study database. The original fax image is also stored. Thus, site personnel can send data to the CSPCC as soon as the forms are completed. DataFax “reads” the fax to interpret and capture the data, then runs the edits to identify inconsistencies (e.g., out-of-range, missing, or inconsistent values). Using a split screen showing the fax image and the interpreted values for a given form page, DataFax uses different colors to identify items that do not pass the edits. Data entry personnel validate the form by comparing the two screens to ensure the entry for each item was interpreted correctly (if not, he/she can make corrections) and attaches a QC note to each item that does not pass edit to indicate the problem. On a regular basis, the CSPCC will use DataFax to produce a QC report that lists all QC notes unresolved during validation and fax the report to the sites. DataFax also keeps track of which QC notes have not been resolved by the sites.

In addition, DataFax facilitates data analysis due to its interface with Statistical Analysis System (SAS) software, Perl (UNIX programming language), and UNIX shell programming.
Other quality control measures include periodic reports containing patient recruitment information and relevant medical data for review by the Principal Proponents.

When data are received at the CSPCC, they will be verified and edited prior to being entered into the main study database. Incomplete or inaccurate data will be returned to the sites for correction using a series of edit reports that are specifically tailored for the study. Sites will resolve data inconsistencies and errors prior to returning data to the CSPCC. All corrections and changes to the data will be reviewed prior to being entered into the main study database. The Principal Proponents and the participating sites will receive periodic reports regarding the quality and quantity of data submitted to the CSPCC.

The CSPCC will also prepare summary reports for the Principal Proponents, the DSMB, and other monitoring groups of the data to track progress, and conduct final analyses of the study data.
VI. MONITORING THE STUDY

A. Organization and Administration

The organizational and administrative structure of this cooperative study will be similar to others in the Cooperative Studies Program. Specifically, it will include the following components:

The Cooperative Studies Program (VA Headquarters) establishes overall policies and procedures which are applied to all VA cooperative studies through the Principal Proponents’ office, and the Palo Alto CSPCC.

The Palo Alto CSPCC and the Principal Proponents’ office jointly will perform the day-to-day scientific and administrative coordination of the study. These include developing the study protocol, operations manual, and case report forms; ensuring the appropriate support for the participating centers; scheduling meetings and conference calls; answering questions about the protocol; conducting site visits; publishing newsletters; preparing interim and final progress reports; and archiving study data at the end of the study. Interim statistical progress reports will be produced every six months. Patient accrual and data quality will be monitored closely to ensure that the study is progressing satisfactorily.

Each participating VA medical center will designate a Site Investigator (SI) to be responsible administratively and scientifically for the conduct of the study at the center. SI’s will be expected to attend all annual Study Group meetings, as well as to hire and supervise personnel. By agreeing to participate in the study, the medical center delegates responsibility for global monitoring of the ongoing study to the DSMB, the Palo Alto CSPCC Human Rights Committee, and the Cooperative Studies Evaluation Committee. However, the Research and Development Committee (R&D) and the Human Studies Subcommittee of the medical center may require the SI to submit annual reports concerning the status of the study at the medical center for local monitoring purposes.
The Cooperative Studies Evaluation Committee (CSEC) reviews the scientific merit of all new cooperative study proposals and all ongoing cooperative studies every three years. The committee is composed of both VA and non-VA clinical research scientists, most of whom have had experience in managing their own cooperative studies.

The **Study Group** will be composed of the SI's from each participating center, the Principal Proponents, and CSP staff (Biostatistician, Clinical Research Pharmacist, Health Economist, and others). The Principal Proponents will head the group, which will meet once per year to discuss the progress of the study, any problems that the investigators have encountered, and any suggestions for improving the study.

The **Executive Committee** will be concerned with the overall management of the study. It will be headed by the Principal Proponents and will consist of the study Biostatistician, Clinical Research Pharmacist, and Health Economist, selected SI's, and outside consultants as needed. This committee will meet every 12 months to review blinded data (not broken down by treatment group), decide upon changes in the study, determine the fate of hospitals whose performance is substandard, initiate any sub-protocols, and discuss publication of the study results.

Interim, independent, and unbiased reviews of the study's ongoing progress will be provided by the **DSMB**. This committee will be composed of a biostatistician and several physicians with expertise in the subject area(s) of the study. The Principal Proponents, study Biostatistician, Clinical Research Pharmacist, and Health Economist, and the Director of the CSPCC and the Chief of the Cooperative Studies Program are ex-officio (liaison, non-voting) members of the committee. The DSMB will meet every 12 months, usually after a meeting of the Study Group and Executive Committee, to monitor the study. Its prime responsibility is to review the progress of the study and to decide whether or not the study should continue. To help them make their assessment, the Principal Proponents and Study Biostatistician will furnish the DSMB with appropriate monitoring data before each meeting.

Part of each DSMB meeting is a joint session held with the **Palo Alto CSPCC Human Rights Committee**. This committee, composed primarily of lay people, is
responsible for ensuring that patients' rights and safety are upheld during the conduct of the study. The committee reviews all new protocols, ongoing studies every 12 months, and periodically makes site visits to participating centers to monitor firsthand the progress of the study. Prior to participation, each site's local R&D and Human Studies Subcommittee must also review and approve it's involvement in the study.

B. Monitoring Patient Intake

The intake rate and operational aspects of this study will be monitored continuously by the Principal Proponents and Study Biostatistician. Participating medical centers will continue in the study only if adequate patient intake is maintained. It is suggested that at the second meeting of the DSMB (approximately 9 months after initiation of patient intake), the study should be considered for possible termination by the DSMB if the study as a whole has not achieved 75% of its expected 9 month patient intake. If a participating medical center has not achieved at least 80% of its expected 9-month patient intake during this period, then it is recommended that the participating medical center be placed on a 90-day probation. If at the end of the probationary period the participating medical center has not randomized an adequate number of additional patients, it should be considered for termination and replacement by another VA medical center. These actions will be taken with the endorsement of the DSMB or by administrative action of the Cooperative Studies Program headquarters.

If recruitment is not proceeding at an appropriate pace, reasons for patient exclusion will be scrutinized by the Principal Proponents and the Study Biostatistician. Based on this information the Executive Committee may choose, with the concurrence of the DSMB, to extend the recruitment period in some or all centers and/or to extend the total length of the study.

C. Monitoring Medical Center Performance

Strict adherence to the protocol will be expected of every participating center and monitored by the DSMB, the Executive Committee and the Study Group.
Documentation of protocol breaches will be required and medical centers with repeated protocol violations will be recommended for termination to the DSMB. If a SI feels that adherence to the protocol will in any way be detrimental to a particular subject's health or well-being, the interest of the patient must take precedence.

By agreeing to participate in the study, the medical center delegates responsibility for global monitoring of the ongoing study to the Cooperative Studies Program committees and personnel listed above. However, the Research and Development (R&D) and the Human Studies Subcommittee (HSS) of the medical center may require the SI to submit annual and final progress reports concerning the status of the study at the medical center for local monitoring purposes.

D. Monitoring Patient Compliance

Patient compliance with PST can be assessed by two modalities of increasing validity. The initial modality (more timely, less valid) is with the routine transtelephonic reporting of INR results which provides a mechanism for ACTIVE surveillance to ensure that patients are continuing to test. The other modality is the meter memory download (substudy sites only) at the time of the quarterly visits (less timely, more valid). These sources will be the basis for the following checks:

1. That the patient is testing within two days of scheduled date
2. Results reported via telephone are concordant with meter memory record (substudy sites only)

Non-Substudy sites that wish to download INR test results from a meter as a means of assessing individual patient compliance, may do so.

E. Monitoring Adverse Events and Serious Adverse Events

1. Adverse Events

Patients will be monitored at each clinic visit and telephone contact for possible adverse events (AE). An AE is defined by the ICH for Clinical Safety Data Management
as any adverse change from the patient’s baseline condition, including any clinical or laboratory test value abnormality, which occurs while the patient is participating in the study. In THINRS, only adverse events determined by the investigator to be related or possibly attributed to the investigative or control intervention, including meter-related and anti-coagulation therapy-related events, will be recorded on an adverse event form. Events that are definitely known to be not related to the meter or anti-coagulation therapy do not need to be recorded as adverse events.

2. Serious Adverse Events

A Serious Adverse Event (SAE) is defined by the ICH for Clinical Safety Data Management and CSP Global Standard Operating Procedure (SOP) 3.6.1, as untoward medical occurrence that at any dose,

- Results in death;
- Is life-threatening;
- Requires inpatient hospitalization or prolongation of existing hospitalization;
- Results in persistent or significant disability or incapacity;
- Is a congenital anomaly/birth defect; or
- Any other condition that, based upon medical judgment, may jeopardize the subject and require medical or surgical treatment to prevent one of the above outcomes.

For THINRS, the SAE’s recorded will be all deaths, regardless of cause; and, all other SAE’s believed by the investigator to be related or possibly attributable to the investigative or control intervention, including meter-related and anti-coagulation therapy-related events. Serious events that are definitely known not to be related to the meter or anti-coagulation therapy do not need to be recorded for the study. SAE’s, including deaths, should be documented on the serious adverse events form.
Expectedness of Serious Events

In general, an unexpected event is considered an event for which the nature, or severity of which, is not consistent with the applicable product information.

As specifically defined in CSP Global SOP 6.3.1, an Unexpected Adverse Event is “an adverse event/reaction, the specificity of which is not consistent with the current investigational brochure or product labeling; or, if an investigator brochure is not required or available, the specificity of severity of which is not consistent with the risk information described in the general investigational plan”.

For Unanticipated Adverse Device Effects (UADE), the following definition is provided by CSP Global SOP 3.6.1: “Any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a meter, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application, or any other unanticipated serious problem associated with a meter that relates to the rights, safety or welfare of subjects”.

For THINRS, both expected and unexpected SAE’s believed by the investigator to be related or possibly attributable to the investigative or control intervention, including meter-related and anti-coagulation therapy related events, should be documented on the serious adverse events form. All deaths, regardless of expectedness, should be documented on the serious adverse events form.

3. Expedited Reporting of Serious Events

Any SAE meeting the definition above requires prompt notification to the Study Co-Chairs and the CSP Clinical Research Pharmacist within 72 hours of the investigator being made aware of the event. Prompt notification of the SAE should be made by faxing a copy of the SAE form to the Site Investigator and the CSP Clinical Research Pharmacy. The FDA and all investigators will be notified if any report suggests a new hazard of which they should be aware.
F. Local Monitoring and Responsibilities

No center should be involved in this study while still participating in another similar study.

By agreeing to participate in the study, the medical centers delegate responsibility for global monitoring of the ongoing study to the CSP committees and personnel described above. However, the Research & Development Committee and the Human Studies Subcommittee of the medical center may require the SI to submit annual and final progress reports concerning the status of the study at that medical center for local monitoring purposes.

G. Monitoring for Premature Termination of the Study

The DSMB makes recommendations to the Chief of the Cooperative Studies Program as to whether the study should continue or be terminated. The decision to terminate a study prematurely is a complex one involving many factors. We suggest that the DSMB consider the following three circumstances as grounds for early termination:

1. If patient accrual falls far below that which is predicted (e.g. 75% of expected accrual), it will be necessary to reassess the study design and the potential value of its continuation.
2. If patient accrual far exceeds the predicted, this study could be completed at an earlier date.
3. If interim analyses indicates a trend in the data which is unlikely to change prior to study completion

Interim analyses will be presented to the DSMB as a guide for such decisions.
VII. PUBLICATIONS

A. Publication Policy

The policy of the Cooperative Studies Program is that outcome data will not be revealed to the SI’s until the data collection phase of the study is completed. This policy safeguards against possible biases affecting the data collection. The regular and ex-officio members of the DSMB and the Palo Alto CSPCC Human Rights Committee will be reviewing the outcome results to ensure that the study will be terminated if a definitive answer is reached earlier than the scheduled end of the study.

All presentations and publications from this study will follow CSPCC policy as stated in the CSP Guidelines. The presentation or publication of any or all data collected by SI’s on patients entered into this VA Cooperative Study is under the direct control of the study’s Executive Committee. This is true whether the publication or presentation is concerned with the results of the principal undertaking or is associated with the study in some other way. No individual SI may perform analyses or interpretations or make public presentations or seek publication of any data unless approved by the Executive Committee.

The Executive Committee has the authority to establish one or more publication committees, usually comprised of subgroups of SI’s and some members of the Executive Committee, for the purpose of producing manuscripts for presentation and publication. Any presentation or publication, when formulated by the Executive Committee or its authorized representatives, should be circulated to all SI’s for review, comments, and suggestions, at least four weeks prior to submission of the manuscript to the presenting or publishing body.

All publications must give proper recognition to the study’s funding source, and should list all participants in the study. If an investigator’s major salary support and/or commitment is from the VA, it is obligatory that investigators list the VA as his/her primary institutional affiliation. Submission of manuscripts or abstracts must follow the usual VA policy; ideally, a subtitle states, “A Department of Veterans Affairs Cooperative
Study.” A copy of the letter to the editor and the manuscript/abstract submitted for
publication or presentation should be sent to the Chief, CSP. The CSP also requires
that every manuscript be reviewed and approved by the Director, CSPCC prior to
submission as a final quality control step. Mechanisms for appeal by any dissatisfied
investigator will follow procedures defined by the VA Medical Research Service.

Participation in Department of Veterans Affairs Cooperative Studies is voluntary.
Any investigator who cannot accept these operational guidelines regarding publication
policy should not volunteer to participate in the study.

B. Anticipated Publications

The following publications are planned:
1. Primary results - An RCT of home INR monitoring versus conventional ACS
2. Impact of INR test frequency on quality of AC
3. Cost-effectiveness of home PT monitoring compared to conventional ACS
4. Factors influencing the quality of AC
5. Relationship between TTR and clinical outcomes: stroke, bleed, myocardial
   infarction, and mortality
6. Satisfaction and quality of life for individuals using home INR monitors

C. Manuscript Committee

The Manuscript Committee will be in charge of publications emanating from the
study. The Manuscript Committee will meet prior to the start of the study, in conjunction
with the Executive Committee, to address any issues related to study publications. The
Manuscript Committee will meet at least once a year thereafter to discuss any relevant
business. At the end of the study, the Manuscript Committee will meet to review the
main study publication, and schedule additional meetings if needed. The Manuscript
Committee will include the Principal Proponents, the CSP Biostatistician, Health
Economist, and Clinical Research Pharmacist, and others.
VIII. HUMAN RIGHTS CONSIDERATIONS

The subject (and caregiver, if needed) must sign the informed consent form for Part 1 of the study and the Health Insurance Portability and Accountability Act (HIPAA) authorization form before they can participate in the study. Generic consent and HIPAA authorization forms are shown in Appendix D.

Informed consent procedures will adhere to VA guidelines. The Study Coordinator (SC) will ensure that the most recent version of the IRB-approved informed consent documents (VA Form 10-1086) is used. A copy of the informed consents can be given to interested subjects to review and discuss with study personnel. Subjects can take a copy of the informed consents home to discuss with family members or their primary physician, without any time limit on when to decide. Study personnel can conduct a follow-up phone call to see if they have made a decision, if the subject has given permission for the call.

For consent obtained face-to-face: The SC will review the informed consent documents with the subject (and caregiver, if present) in a location providing privacy, discuss all elements of the documents, provide an overview of the study, and explain the purpose, procedures, visit schedule, risks, and benefits of study participation. The SC will allow the subject/caregiver time to read the consent forms and ask questions, and encourage input from family members and other care providers, if appropriate. The subject/caregiver may then voluntarily consent free of coercion and without undue influence, recognizing a right to withdraw from the study at any time without penalty. During the consent process, be sure to discuss the following:

- The importance of following study procedures.
- The importance of compliance with all assessments and study visits.
- The possibility of the need for unscheduled visits (i.e., for supplies).
- Meter and all unused cuvettes MUST be brought to the clinic for follow-up appointments. The appointment will have to be rescheduled if the subject forgets to bring either of these items.
For consent obtained by mail: Subjects who take the consent home and later decide to participate in the study can return the consent form by mail. Remind the subject to sign the final page, initial all other pages and date the informed consent form before returning. Document when the reminder to return the consent form is given on the Tracking Worksheet for Mailed Informed Consent. Give the subject 2 copies to take home: one to keep, and the other to sign and mail back. The subject’s signature must be witnessed by someone who is not a study staff member. A note should be placed in the subject’s chart by the Site Investigator or Study Coordinator when the consent form is received stating that the subject is enrolled in THINRS.

After consenting the subject/caregiver to participate in the study, the SC will:

- Ensure that the subject (or the subject's legal representative)/caregiver signs the final page of the forms, initials all other pages and dates the documents. The person who obtains consent (often the SC), the Site Investigator (SI), and a witness not associated with the study must also sign the final page of each form on the appropriate signature lines.
- Write the subject’s/caregiver’s name and date on the top of each page of the consent documents, and write the subject’s/caregiver’s name (last, first and middle initial) and identification number (SSN) for the subject only (not needed for the caregiver) on the bottom panel of the first page of each form.
- Make 4 copies each of the signed informed consent and HIPAA authorization forms, and provide one to the subject, send one copy to medical records, one to the Pharmacy Service, and mail the final copy to the Palo Alto CSPCC. The original informed consent and HIPAA authorization document goes in the subject’s research record.
- If a caregiver consent and HIPAA authorization is required, write the seven-digit patient identification number (patient ID) in the top margin of each page of the caregiver’s consent and HIPAA authorization forms. Then, make 2 copies and provide one to the caregiver and mail a copy to the Palo Alto CSPCC. The original informed consent and HIPAA authorization documents go in the subject’s study file.
Consent for Part 1 (Part 2) must be obtained prior to initiating any subject-related procedures for that part of the study.

The following are the consent forms for subjects/caregivers in Parts 1 and 2.
A. Subject Consent for Part 1

You are invited to take part in a research study at the______________________ Department of Veterans Affairs Medical Center.

1. Background and Purpose:

Because you take a blood thinning drug (anticoagulant) called warfarin (also known as Coumadin), you should know that you must be monitored closely because too much drug may increase your risk of bleeding and too little drug may increase your risk of getting a blood clot. The usual way to monitor the level of warfarin is to take a blood sample and check it in a laboratory. Portable machines to measure the same thing from a fingerstick sample of blood have been approved for home use by the Food and Drug Administration (FDA) since 1997.

This study, Part 1 of Cooperative Study (CS) 481 or THINRS, has two purposes which are equally important. One goal is to determine if patients like you can perform their own tests at home using portable machines. The other is to help identify patients who may be invited to be in a three-year study (Part 2 of CS #481) to do a long-term test of these machines. The three-year study will compare standard anticoagulation monitoring (at the clinic) to patients doing their own testing at home. So, if you are in the three-year study, you may not be assigned to do your own testing at home.

2. Study Procedures:

Part 1 will include about 4000 patients in 32 VA Medical Centers, with up to 300 patients from this medical center. Your participation in this study will last for 2 to 4 weeks. You will receive extensive training on how to do a fingerstick on yourself to get a blood sample and on the care and use of the machine and its supplies. This training may include a videotape, lecture, and written documentation as well as “hands on” practice on using the machine. The training will last about two hours.
During the training visit, once you demonstrate that you can use the machine correctly and get a test result, the VA clinic staff will do a repeat test and compare its results to those from your test. You will then get a diary and a testing kit to take home for two weeks. You will be asked to do the tests at home twice a week (total of 4 times) and to record the result of each test in the diary and report the results by telephone to an automated answering service. At the end of two weeks you will be asked to return to the clinic to do a test in front of the clinical staff and to have the VA clinic staff repeat the test and compare its results to those from your test. If these results show that you can do testing at home properly, you will have finished your participation in Part 1. If the study staff feel you need more training and you are willing to continue in Part 1, you will be asked to do home testing twice a week for two more weeks, record the results in a diary and report the results by telephone to an automated answering service, and return to the clinic at the end of that period to do a test in front of the clinical staff and to have the VA clinic staff repeat the test and compare its results to those from your test. So, over the course of Part 1, you will visit the clinic 2 to 3 times, give one blood sample and have a total of 2 to 3 fingerstick tests done by the staff and a total of 6 to 11 fingerstick tests done by you.

It is important for your safety that you follow the schedule when doing the tests and report the results accurately.

In addition to completing the training to do the home testing, you will also be asked to complete a few questionnaires about your ability to follow study procedures.

Note that you must not change your warfarin (Coumadin) dose on your own at any time during this study.

If the test results you obtain at home are outside the range assigned by your doctor, you should contact the study staff for advice.

You will be required to return the home testing meter at the conclusion of your participation.

3. Risks and Discomforts:

Part 1 includes only standard procedures used to monitor warfarin treatment: fingerstick blood samples and laboratory blood drawing. A fingerstick may cause some pain and if not done correctly may cause infection. Laboratory blood drawing (using a needle in a vein) may cause pain and minor bruising around where the needle is inserted and dizziness once you stand up after the blood is drawn.

While it is hard to predict every possible risk from being in this study, it is unlikely that there will be any serious problems since the study has no experimental procedures.

4. Potential Benefits:

You may not receive any direct benefits from being in this study other than the training you will receive. You may get indirect benefit if this study leads to better ways to monitor anticoagulation.

Patient’s Initials
5. Other Treatment Available:

This study includes both standard procedures used to monitor warfarin treatment (fingerstick blood samples and laboratory blood drawing); there are no other accepted methods. You will receive your current health care and anticoagulation monitoring if you decide not to take part in this study.

6. Study Follow-up and Special Circumstances:

Other than the chance to be in the three-year study of the monitoring machines (Part 2 of CS #481), there is no follow-up for this study. There are no special circumstances related to this study.

7. Withdrawal from the Study:

Your participation in this research is voluntary. You do not have to take part in this study and you may quit at any time by telling a member of the study staff. Your decision not to participate or to withdraw will have no effect on your rights to any benefits to which you are entitled.

Research staff may end your study participation at any time if they feel it is in your best interests or if you do not follow the study procedures.

8. Confidentiality and Use of Research Results:

Participation in this study will be kept confidential. Neither your name, initials, nor other identifying data will be released or published without your permission unless we are required to do so by law. Data entered into a computer will be stored using a study patient identification code that does not identify you by name, and only selected researchers associated with the study will have access to this information. We will link your Social Security Number (SSN) with your study patient identification code to get information on your use of VA health care services. However, the list with your SSN and all data collection forms will be kept in a secure place. If the results of this study are reported in a medical journal or at meetings, you will not be identified by name, or by any other means without your written consent.

9. Special Information:

a. There will be no cost to you for any of the treatment or testing done as part of this research study.

b. Eligibility for medical care is based on the usual VA eligibility policy and is not affected by participation in a research study.

c. In the event of bad effects or physical injury resulting from participation in this research study, you will get emergency medical treatment. If you believe that you received an injury from participation in this research study, you should contact Dr. ___________, the physician and Site investigator of the study, by calling ____________.

Patient initials

10-1086
Subject Name: _____________________________ Date: ______________

Title of Study: The Home INR Study – Part 1

Principal Investigator: ___________________ VAMC: ___________________

Eligible veterans are entitled to medical care and treatment in accordance with federal law. Non-eligible veterans can receive medical care and treatment from the VA for injury resulting from participation in this research study unless the injury is due to the patient not following the study procedures.

Further information about compensation may be obtained from the Medical Administration Service at the _____________ VA Medical Center.

d. If you have any questions about your rights you may contact the Administrative Officer of the Research Service at ____________.

e. If you are in other research studies, you must discuss the implications of this situation with the directors of all of the studies. By signing the last page of this form, you indicate that you have had these discussions.

f. You will be told about any significant new findings that could affect your willingness to participate or continue to participate in this study.

g. If you decide to participate, please sign the last page of this form indicating that you understand the risks, benefits and purpose of this study.

Patient’s Initials

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Subject Name: __________________________ Date: __________

Title of Study: The Home INR Study – Part 1

Principal Investigator: __________________________ VAMC: __________

RESEARCH PATIENTS’ RIGHTS:

I have read or have had read to me all of the above. Dr. _______________________ has explained the research study to me and answered all of my questions. I have been told of the risks or discomforts and possible benefits of the research study. I have been told of other choices of treatment available to me.

I authorize the use of my blood without payment for this study.

I understand that I do not have to take part in this research study, and my refusal to participate will involve no penalty or loss of rights to which I am entitled. I may withdraw from this research study at any time, and if I am a Veteran, I may do so without penalty or loss of VA or other benefits to which I am entitled.

The results of this research study may be published, however, I will not be identified by name or other personal identifiers. Further, my records will not be revealed unless required by law.

In case there are medical problems or questions, I have been told I can call:

Dr. ________________________ at __________________ during the day, and
Dr. ________________________ at __________________ after hours.

If any medical problems occur in connection with this research study the VA will provide emergency care.

I understand my rights as a research patient, and I voluntarily consent to participate in this research study. I understand what the research study is about and how and why it is being done. I will receive a signed copy of this consent form.

Patient’s Signature __________________________ Date __________

Signature of Witness __________________________ Witness (print) __________________________

Signature of Investigator __________________________ Date __________

Signature of Person Obtaining Consent __________________________ Date __________

Signature of Investigator __________________________ Date __________

IF MORE THAN ONE PAGE IS USED, EACH PAGE (VAF 10-1086A) MUST BE CONSECUTIVELY NUMBERED AND SIGNED.

VA FORM JAN 1990 10-1086
B. Subject Consent for Part 2

Subject Name: ___________________________ Date: __________________

Title of Study: The Home INR Study - Part 2

Principal Investigator: ___________________________ VAMC: __________________

DESCRIPTION OF RESEARCH:
You are invited to take part in a research study at the ________________ Department of Veterans Affairs Medical Center.

1. Background and Purpose:
   Because you take a blood thinning drug (anticoagulant) called warfarin (also known as Coumadin), you should know that you must be monitored closely because too much drug may increase your risk of bleeding and too little drug may increase your risk of getting a blood clot. The usual way to monitor the level of warfarin is to take a blood sample and check it in a laboratory. Portable machines to measure the same thing from a fingerstick sample of blood have been approved for home use by the Food and Drug Administration (FDA) since 1997.
   This study, Part 2 of Cooperative Study (CS) 481 or THINRS, will include patients like you who can perform their own tests at home using portable machines. The study will test if home testing can increase the effectiveness of warfarin therapy by reducing the incidence of blood clots or bleeding problems when compared to standard anticoagulation monitoring in a medical center or clinic.

2. Study Procedures:
The study will include about 3200 patients in 32 VA Medical Centers, with up to 300 patients from this medical center. Your participation in this study will last for 2 to 3 years. In a prior study you received extensive training on how to do a fingerstick on yourself to get a blood sample and on the care and use of the machine and its supplies.

   INCLUDE THIS PARAGRAPH FOR SITES NOT IN TESTING FREQUENCY SUBSTUDY: You will be randomly assigned to one of two groups. Patients in Group 1 will get standard anticoagulation monitoring, which means they will have their tests done about once every 4 weeks by the professional staff of the anticoagulation management service (also called Coumadin Clinic or Anticoagulation Clinic) or the hospital laboratory. Patients in Group 2 will do tests at home about once a week. You have a 1 in 2 chance of being assigned to Group 1 and the same odds for Group 2.

SUBJECT’S IDENTIFICATION (I.D. plate or give name-last, first, middle)

____________________________
Patient’s Initials

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INCLUDE THE FOLLOWING FOR SITES IN TESTING FREQUENCY SUBSTUDY: You will be randomly assigned to one of four groups using a two-stage process. In the first stage, you have a 1 in 2 chance of being assigned to Group 1. Patients in Group 1 will have their tests done about once every 4 weeks by the professional staff of the anticoagulation management service (also called Coumadin Clinic or Anticoagulation Clinic) or the hospital laboratory. You also have a 1 in 2 chance of being assigned to do home testing in the first stage. In the second stage, those assigned to home testing in the first stage will be assigned either to do the tests about once a week (Group 2), about twice a week (Group 3), or about once every 4 weeks (Group 4). So, if assigned to home testing, you have a 1 in 3 chance of being assigned to Group 2 and the same odds for each of Groups 3 and 4.

At the start of the study you will be asked to answer questions about your medical history and the drugs you are taking and to fill out several forms which should take about one hour to complete. You will also need to undergo an electrocardiogram (ECG) if you have not had one recently. Every three months for the next 2-3 years you will be asked to report on your health and any medical problems you have had, and to provide information about medical care that you receive from providers (for example, doctors or hospitals) that are not part of the VA. If you were hospitalized, we will ask the providers to give us more information (for example, the number of days you were in the hospital and the reason you were hospitalized) about the care you received if you give your consent for us to see your medical and billing records. For each instance when you were hospitalized outside of the VA, you will need to sign the form "Consent to the Release of Non-VA Medical and Billing Records" which appears as the last page of this document.

If you are in Group 1 (standard anticoagulation monitoring), you will get medical care according to standard practice with testing done in the clinic about once every 4 weeks. You may get testing more often depending on your medical condition. If possible, we will schedule your quarterly visit with the study coordinator to occur with one of your “every 4 weeks” anticoagulation monitoring visits.

INCLUDE THIS PARAGRAPH FOR SITES NOT IN TEST FREQUENCY SUBSTUDY: If you are in Group 2 (Home Testing), you will get a diary and a testing kit to take home. You will be asked to perform tests at home once a week. You may be asked to do testing more often depending on your medical condition. You will record the results of each test in the diary and report the results by telephone to an automated answering service each time you do a test. Once every three months you will be asked to return to the clinic and to bring the diary and machine with you. At the clinic you will have 3 fingerstick tests done. You will do the first test using your machine. The research staff will do the second test using your machine and the third using the clinic’s machine, then compare the results from the 3 tests. The results from the fingerstick tests will also be compared to those from the laboratory analysis of your blood samples. The research staff will collect the diary and give you a new diary (to write down future test results) and additional supplies. It is important for your safety that you follow the schedule when doing the tests and report the results accurately.

__________________________

Patient’s Initials
INCLUDE THIS PARAGRAPH FOR SITES IN TEST FREQUENCY SUBSTUDY: If you are in Group 2, 3, or 4 (Home Testing), you will get a diary and a testing kit to take home. You will be asked to perform tests at home at the interval indicated for your group (once a week for Group 2, twice a week for Group 3, and once every 4 weeks for Group 4). You may be asked to do testing more often depending on your medical condition. You will record the results of each test in the diary and report the results by telephone to an automated answering service each time you do a test. Once every three months you will be asked to return to the clinic and to bring the diary and machine with you. At the clinic you will have 3 fingerstick tests done. You will do the first test using your machine. The research staff will do the second test using your machine and the third using the clinic's machine, then compare the results from the 3 tests. The results from the fingerstick tests will also be compared to those from the laboratory analysis of your blood samples. The research staff will collect the diary, download information from the machine, and give you a new diary (to write down future test results) and additional supplies. It is important for your safety that you follow the schedule when doing the tests and report the results accurately.

Note that you must not change your warfarin (Coumadin) dose on your own at any time during this study.

If your test results are outside the range assigned by your doctor, you should contact the study staff for advice.

If assigned to home testing, you may be asked to return the home testing meter at the conclusion of your participation in the study under certain conditions (for example, if the Site Investigator or your doctor feels that continued use of the meter is not in your best interests).

3. Risks and Discomforts:
   This study includes only standard procedures used to monitor warfarin treatment: fingerstick blood samples and laboratory blood drawing. A fingerstick may cause some pain and if not done correctly may cause infection. Laboratory blood drawing (using a needle in a vein) may cause pain and minor bruising around where the needle is inserted and dizziness once you stand up after the blood is drawn.
   While it is hard to predict every possible risk from being in this study, it is unlikely that there will be any serious problems since the study has no experimental procedures.

4. Potential Benefits:
   You may not receive any direct benefits from being in this study other than from the training that you will receive. You may benefit if this study leads to better ways to monitor anticoagulation.
Subject Name: ____________________________ Date: ________________

Title of Study: The Home INR Study – Part 2

Principal Investigator: ____________________________ VAMC: ________________

5. Other Treatment Available:
   This study includes both standard procedures used to monitor warfarin treatment (fingerstick blood samples and laboratory blood drawing); there are no other accepted methods. You will receive your current health care and anticoagulation monitoring if you decide not to take part in this study.

6. Study Follow-up and Special Circumstances:
   There is no follow-up or special circumstances related to this study.

7. Withdrawal from the Study:
   Your participation in this research is voluntary. You do not have to take part in this study and you may quit at any time by telling a member of the study staff. Your decision not to participate or to withdraw will have no affect on your rights to any benefits to which you are entitled.
   Research staff may end your study participation at any time if they feel it is in your best interests or if you do not follow the study procedures.

8. Confidentiality And Use of Research Results:
   Participation in this study will be kept confidential. Neither your name, initials, nor other identifying data will be released or published without your permission unless we are required to do so by law. Data entered into a computer will be stored using a study patient identification code that does not identify you by name, and only selected researchers associated with the study will have access to this information.
   We will link your Social Security Number (SSN) with your study patient identification code to get information on your use of VA health care services. However, the list with your SSN and all data collection forms will be kept in a secure place. If the results of this study are reported in a medical journal or at meetings, you will not be identified by name or by any other means.
   In addition to collecting information from you and your medical record, we will obtain data from centralized VA databases. These are electronic versions of selected information in your medical records, including data on all VA health care services you have received at this or other VA facilities. These electronic databases will be our primary source of information for use of all health care services for the economic analysis. We will also use the electronic data to collect information on the VA's distribution to you of prescription medications.

__________________________
Patient’s Initials
Subject Name: __________________________ Date: ____________

Title of Study: The Home INR Study – Part 2

Principal Investigator: __________________________ VAMC: __________________________

9. Special Information:
   a. There will be no cost to you for any of the treatment or testing done as a part of this research study.
   b. Eligibility for medical care is based on the usual VA eligibility policy and is not affected by participation in a research study.
   c. In the event of bad effects or physical injury resulting from participation in this study, you will get emergency medical treatment. If you believe that you received an injury from participation in this research study, you should contact Dr. ____________, the physician and Site investigator of the study, by calling _____________.

   Eligible veterans are entitled to medical care and treatment in accordance with federal law. Non-eligible veterans can receive medical care and treatment from the VA for injury resulting from participation in this study unless the injury is due to the patient not following the study procedures.

   Further information about compensation may be obtained from the Medical Administration Service at the ____________ VA Medical Center.

   d. If you have any questions about your rights you may contact the Administrative Officer of the Research Service at _____________.

   e. If you are in other research studies, you must discuss the implications of this situation with the directors of all of the studies. By signing the last page of this form, you indicate that you have had these discussions.

   f. You will be told about any significant new findings that could affect your willingness to participate or continue to participate in this study.

   g. If you decide to participate, please sign the last page of this form indicating that you understand the risks, benefits and purpose of this study.

__________________________
Patient’s Initials
Subject Name: __________________________ Date: ________________

Title of Study: The Home INR Study – Part 2 __________________________

Principal Investigator: __________________________ VAMC: ___________

RESEARCH PATIENTS' RIGHTS:

I have read or have had read to me all of the above. Dr. __________________________ has explained the research study to me and answered all of my questions. I have been told of the risks or discomforts and possible benefits of the research study. I have been told of other choices of treatment available to me.

I authorize the use of my blood without payment for this study.

I understand that I do not have to take part in this research study, and my refusal to participate will involve no penalty or loss of rights to which I am entitled. I may withdraw from this research study at any time, and if I am a Veteran, I may do so without penalty or loss of VA or other benefits to which I am entitled.

The results of this research study may be published, however, I will not be identified by name or other personal identifiers. Further, my records will not be revealed unless required by law. In case there are medical problems or questions, I have been told I can call:

Dr. __________________________ at __________________________ during the day, and
Dr. __________________________ at __________________________ after hours.

If any medical problems occur in connection with this research study the VA will provide emergency care.

I understand my rights as a research patient, and I voluntarily consent to participate in this research study. I understand what the research study is about and how and why it is being done. I will receive a signed copy of this consent form.

______________________________ ___________________
Patient’s Signature Date

_______________________________ ___________________________________
Signature of Witness Witness (print)

_______________________________        ____________________
Signature of Investigator                                Date

_______________________________        ____________________
Signature of Person Obtaining Consent        Date

_______________________________        ____________________
Signature of Investigator                               Date

IF MORE THAN ONE PAGE IS USED, EACH PAGE (VAF 10-1086A) MUST BE CONSECUTIVELY NUMBERED AND SIGNED.

VA FORM 10-1086
CONSENT TO THE RELEASE OF NON-VA MEDICAL AND BILLING RECORDS:
This form documents that I, _____________________, have agreed to be in VA Cooperative Study
#481, "Home INR Monitoring", and I agree that researchers working on the study may get copies of
my medical and billing records from non-VA providers. I have been told of all risks from being in this
study, and I have signed the consent form which is in my medical records at the ______________
VA Medical Center.

The specific purpose of this form is to let the VA Cooperative Studies Program get information about
my inpatient hospitalization at
(name of hospital or clinic)_________________________
on or about (range of dates) _______________________.

___________________ __________________________  __________
Print name  Signature     Date
C. Caregiver Consent for Part 1

**Department of Veterans Affairs**

**VA RESEARCH CONSENT FORM**

<table>
<thead>
<tr>
<th>Subject Name:</th>
<th>Date:</th>
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**Title of Study:** The Home INR Study - Part 1 - Caregiver

**Principal Investigator:**

**VAMC:**

**DESCRIPTION OF RESEARCH BY INVESTIGATOR:**

As caregiver of the veteran listed above, you are invited to take part in a research study at the______________________ Department of Veterans Affairs Medical Center.

This document explains what is required of you and your relative/friend to participate in this study because your relative/friend needs your help to perform some of the study procedures.

1. **Background and Purpose:**

   Because your relative/friend takes a blood thinning drug (anticoagulant) called warfarin (also known as Coumadin), your relative/friend must be monitored closely because too much drug may increase the risk of bleeding and too little drug may increase the risk of getting a blood clot. The usual way to monitor the level of warfarin is to take a blood sample and check it in a laboratory. Portable machines to measure the same thing from a fingerstick sample of blood have been approved for home use by the Food and Drug Administration (FDA) since 1997. This study, Part 1 of Cooperative Study (CS) 481 or THINRS, has two purposes which are equally important. One goal is to determine if you and patients like your relative/friend can perform their own tests at home using portable machines. Your relative/friend has asked that you learn to perform the test with him/her. The other is to help identify patients and their caregivers who may be invited to be in a three-year study, Part 2 of CS #481, to do a long-term test of these machines. The three-year study will compare standard anticoagulation monitoring (at the clinic) to patients and their caregivers doing testing at home. So, if you and your relative/friend are in the three-year study, you may not be assigned to do testing at home.

2. **Study Procedures:**

   Part 1 will include about 4000 patients in 32 VA Medical Centers, with up to 300 patients from this medical center. Your relative/friend’s participation in this study will last for 2 to 4 weeks. You will receive extensive training on how to do a fingerstick on your relative/friend to get a blood sample and on the care and use of the machine and its supplies. This training may include a videotape, lecture, and written documentation as well as “hands on” practice on using the machine. The training will last about two hours.

 PRIVILEGED AND CONFIDENTIAL;5/18/2006; 87
During the training visit, once you demonstrate that you can use the machine correctly and get a test result, the VA clinic staff will do a repeat test and compare its results to those from your test. You will then get a diary and a testing kit to take home for two weeks. You will be asked to do the tests on your relative/friend at home twice a week (total of 4 times) and to record the result of each test in the diary and report the results by telephone to an automated answering service. If these results show that you and your relative/friend can do testing at home properly, you and your relative/friend will have finished participation in Part 1. If the study staff feel more training is needed and you and your relative/friend are willing to continue in Part 1, you will be asked to do home testing twice a week for two more weeks, record the results in a diary and report the results by telephone to an automated answering service, and return to the clinic at the end of that period to do a test in front of the clinical staff and to have the VA clinic staff repeat the test and compare its results to those from your and your relative/friend's test. So, over the course of Part 1, you and your relative/friend will visit the clinic 2 to 3 times, your relative/friend will give one blood sample and have a total of 2 to 3 fingerstick tests done by the staff and a total of 6 to 11 fingerstick tests done by you.

It is important for the safety of your relative/friend that you follow the schedule when doing the tests and report the results accurately.

In addition to completing the training to do the home testing, you will also be asked to complete a few questionnaires about your ability to follow study procedures.

Note that you and your relative/friend must not change his/her warfarin (Coumadin) dose on your own at any time during this study.

If the test results obtained at home are outside the range assigned by your relative’s/friend’s doctor, you should contact the study staff for advice.

You will be required to return the home testing meter at the conclusion of your participation.

3. Risks and Discomforts:

When performing the fingerstick test, you will be exposed to the blood of your relative/friend. This puts you at risk for catching a disease that might be carried in the blood. You will be taught ways to protect yourself from possible diseases while doing the test, such as washing your hands and wearing gloves. Because of the way the fingerstick tool is made, it would be very hard to accidentally stick yourself. If this does happen, you should wash the cut with soap and water. There may be slight bruising around the cut for a day or two.

For your relative/friend, this study includes only standard procedures used to monitor warfarin treatment: fingerstick blood samples and laboratory blood drawing. A fingerstick may cause some pain and if not done correctly may cause infection. Laboratory blood drawing (using a needle in a vein) may cause pain and minor bruising around where the needle is inserted and dizziness once your relative/friend stands up after the blood is drawn.

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Patient’s Initials

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Subject Name: _______________________________________________ Date: ________________

Title of Study: The Home INR Study – Part 1 - Caregiver

Principal Investigator: _________________________________________ VAMC: ________________

While it is hard to predict every possible risk from being in this study, it is unlikely that there will be any serious problems since the study has no experimental procedures.

4. Potential Benefits:
   You and your relative/friend may not receive any direct benefits from being in this study other than the training you will receive. You and your relative/friend may get indirect benefit if this study leads to better ways to monitor anticoagulation.

5. Other Treatment Available:
   This study includes both standard procedures used to monitor warfarin treatment (fingerstick blood samples and laboratory blood drawing); there are no other accepted methods. Your relative/friend will receive his/her current health care and anticoagulation monitoring if you decide not to take part in this study.

6. Study Follow-up and Special Circumstances:
   Other than the chance to be in the three-year study of the monitoring machines (Part 2 of CS #481), there is no follow-up for this study. There are no special circumstances related to this study.

7. Withdrawal from the Study:
   Your participation in this research is voluntary. You do not have to take part in this study and you may quit at any time by telling a member of the study staff. Your decision not to participate or to withdraw will have no effect on your relative’s/friend’s rights to any benefits to which they are entitled.

   Research staff may end your study participation at any time if they feel it is in your relative’s/friend’s best interests or if you do not follow the study procedures.

8. Confidentiality and Use of Research Results:
   Participation in this study will be kept confidential. Neither your name, initials, nor other identifying data will be released or published without your permission unless we are required to do so by law. Data entered into a computer will be stored using a study patient identification code that does not identify your relative/friend by name, and only selected researchers associated with the study will have access to this information. We will link the Social Security Number (SSN) of your relative/friend with his/her study patient identification code to get information on use of VA health care services. However, the list of SSNs and all data collection forms will be kept in a secure place. If the results of this study are reported in a medical journal or at meetings, neither you nor your relative/friend will be identified by name, or by any other means without your written consent.

________________________
Patient’s Initials

PRIVILEGED AND CONFIDENTIAL; 5/18/2006; 89
Subject Name: ___________________________ Date: __________________

Title of Study: The Home INR Study – Part 1 - Caregiver

Principal Investigator: ___________________________ VAMC: ____________

9. Special Information:
   a. There will be no cost to you or your relative/friend for any of the treatment or testing done as part of this research study.
   b. Eligibility for medical care is based on the usual VA eligibility policy and is not affected by participation in a research study.
   c. In the event of bad effects or physical injury resulting from participation in this research study, you will get emergency medical treatment. If you believe that you received an injury from participation in this research study, you should contact Dr. ____________, the physician and Site investigator of the study, by calling ____________.
   
   If you are an eligible veteran, you are entitled to medical care and treatment in accordance with federal law. If you are a non-eligible veteran, you can receive medical care and treatment from the VA for injury resulting from participation in this research study unless the injury is due to you not following the study procedures.
   
   Further information about compensation may be obtained from the Medical Administration Service at the ____________ VA Medical Center.
   
   d. If you have any questions about your rights or those of your relative/friend, you may contact the Administrative Officer of the Research Service at ____________.
   
   e. You will be told about any significant new findings that could affect your willingness or that of your relative/friend to participate or continue to participate in this study.
   
   f. If you decide to participate, please sign the last page of this form indicating that you understand the risks, benefits and purpose of this study.
Subject Name: 

Date: 

Title of Study: The Home INR Study – Part 1 - Caregiver 

Principal Investigator: ______________________ VAMC: ______________________

RESEARCH PATIENTS’ RIGHTS:

I have read or have had read to me all of the above. Dr. ______________________ has explained the research study to me and answered all of my questions. I have been told of the risks or discomforts and possible benefits of the research study. I have been told of other choices of treatment available to me.

I understand that I do not have to take part in this research study, and my refusal to participate will involve no penalty or loss of rights to which I am entitled. I may withdraw from this research study at any time, and if I am a Veteran, I may do so without penalty or loss of VA or other benefits to which I am entitled.

The results of this research study may be published, however, I will not be identified by name or other personal identifiers. Further, my records will not be revealed unless required by law.

In case there are medical problems or questions, I have been told I can call:
Dr. ______________________ at ______________________ during the day, and
Dr. ______________________ at ______________________ after hours.

If any medical problems occur in connection with this research study the VA will provide emergency care.

I understand my rights as a research patient, and I voluntarily consent to participate in this research study. I understand what the research study is about and how and why it is being done. I will receive a signed copy of this consent form.

Caregiver’s Signature ______________________ Date ______________________

Signature of Witness ______________________ Witness (print) ______________________

Signature of Investigator ______________________ Date ______________________

Signature of Person Obtaining Consent ______________________ Date ______________________

IF MORE THAN ONE PAGE IS USED, EACH PAGE (VAF 10-1086A) MUST BE CONSECUTIVELY NUMBERED AND SIGNED.
Subject Name: ___________________________ Date: __________________

Title of Study: The Home INR Study - Part 2 - Caregiver

Principal Investigator: VAMC:

DESCRIPTION OF RESEARCH:

As caregiver of the veteran listed above, you are invited to take part in a research study at the Department of Veterans Affairs Medical Center. This document explains what is required of you and your relative/friend to participate in this study because your relative/friend needs your help to perform some of the study procedures.

1. Background and Purpose:

Because your relative/friend takes a blood thinning drug (anticoagulant) called warfarin (also known as Coumadin), you should know that your relative/friend must be monitored closely because too much drug may increase the risk of bleeding and too little drug may increase the risk of getting a blood clot. The usual way to monitor the level of warfarin is to take a blood sample and check it in a laboratory. Portable machines to measure the same thing from a fingerstick sample of blood have been approved for home use by the Food and Drug Administration (FDA) since 1997.

This study, Part 2 of Cooperative Study (CS) 481 or THINRS, will include patients who can do their own testing at home using portable machines and patients like your relative/friend who have someone to help perform these tests. The study will test if home testing can increase the effectiveness of warfarin therapy by reducing the incidence of blood clots or bleeding problems when compared to standard anticoagulation monitoring in a medical center or clinic.

2. Study Procedures:

The study will include about 3200 patients in 32 VA Medical Centers, with up to 300 patients from this medical center. Your participation in this study will last for 2 to 3 years. In a prior study you received extensive training on how to do a fingerstick on your relative/friend to get a blood sample and on the care and use of the machine and its supplies.
Subject Name: ______________________________ Date: __________________

Title of Study: The Home INR Study – Part 2 - Caregiver

Principal Investigator: ___________________________ VAMC: __________________

INCLUDE THIS PARAGRAPH FOR SITES NOT IN TESTING FREQUENCY SUBSTUDY: You will be randomly assigned to one of two groups. Patients in Group 1 will receive standard anticoagulation monitoring, which means they will have their tests done about once every 4 weeks by the professional staff of the anticoagulation management service (also called Coumadin Clinic or Anticoagulation Clinic) or the hospital laboratory. Patients in Group 2 will have tests done at home about once a week. Your relative/friend will have a 1 in 2 chance of being assigned to Group 1 and the same odds for Group 2.

INCLUDE THIS PARAGRAPH FOR SITES IN TESTING FREQUENCY SUBSTUDY: You will be randomly assigned to one of four groups using a two-stage process. In the first stage, you have a 1 in 2 chance of being assigned to Group 1. Patients in Group 1 will receive standard anticoagulation monitoring, which means they will have their tests done about once every 4 weeks by the professional staff of the anticoagulation management service (also called Coumadin Clinic or Anticoagulation Clinic) or the hospital laboratory. You also have a 1 in 2 chance of being assigned to do home testing in the first stage. In the second stage, those assigned to home testing will be assigned either to do the tests about once a week (Group 2), about twice a week (Group 3), or about once every 4 weeks (Group 4). So, if assigned to home testing, you have a 1 in 3 chance of being assigned to Group 2 and the same odds for each of Groups 3 and 4.

At the start of the study your relative/friend will be asked to answer questions about their medical history and the drugs they are taking and to fill out several forms which should take about one hour to complete. He/she will also need to undergo an electrocardiogram (ECG) if he/she has not had one recently. Every three months for the next 2-3 years you and your relative/friend will be asked to report on their health and any medical problems they have had, and to provide information about medical care that they have received from providers (for example, doctors or hospitals) that are not part of the VA. You will also be asked to complete several forms which report on the care your relative/friend received over the past three months. If your relative/friend was hospitalized, we will ask the providers to give us more information (for example, the number of days your relative/friend was in the hospital and the reason they were hospitalized) about the care they received if they give their consent for us to see their medical and billing records. For each instance when your relative/friend was hospitalized outside of the VA, s/he will need to sign the form “Consent to the Release of Non-VA Medical and Billing Records” which appears as the last page of this document.

If assigned to Group 1 (standard anticoagulation monitoring), your relative/friend will get medical care according to standard practice with testing done in the clinic about once every 4 weeks. Your relative/friend may get testing more often depending on his/her medical condition. If possible, we will schedule your quarterly visit with the study coordinator to occur with one of your “every 4 weeks” anticoagulation monitoring visits.

____________________________
Patient’s Initials
<table>
<thead>
<tr>
<th>Subject Name:</th>
<th>Date:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Title of Study:</td>
<td>The Home INR Study – Part 2 - Caregiver</td>
</tr>
<tr>
<td>Principal Investigator:</td>
<td>VAMC:</td>
</tr>
</tbody>
</table>

**INCLUDE THIS PARAGRAPH FOR SITES NOT IN THE TESTING FREQUENCY SUBSTUDY:**
If assigned to Group 2 (Home Testing), your relative/friend will get a diary and a testing kit to take home. You will be asked to perform tests on your relative/friend at home once a week. You may be asked to do testing more often depending on your relative/friend’s medical condition. You will record the results of each test in the diary and report the results by telephone to an automated answering service each time you do a test on your relative/friend. Once every three months you and your relative/friend will be asked to return to the clinic and to bring the diary and machine with you. At the clinic your relative/friend will have 3 fingerstick tests done. You will do the first test on your relative/friend using your machine. The research staff will do the second test using your machine and the third using the clinic’s machine, then compare the results from the 3 tests. The results from the fingerstick tests will also be compared to those from the laboratory analysis of your relative’s/friend’s blood samples. The research staff will collect the diary, and give you a new diary (to write down future test results) and additional supplies. It is important for the safety of your relative/friend that you follow the schedule when doing the tests and report the results accurately.

**INCLUDE THIS PARAGRAPH FOR SITES IN TESTING FREQUENCY SUBSTUDY:**
If assigned to do Home Testing, your relative/friend will get a diary and a testing kit to take home. You will be asked to perform tests on your relative/friend at home at the interval indicated for your group (once a week for Group 2, twice a week for Group 3, and once every 4 weeks for Group 4). You may be asked to do testing more often depending on your relative/friend’s medical condition. You will record the results of each test in the diary and report the results by telephone to an automated answering service each time you do a test on your relative/friend. Once every three months you and your relative/friend will be asked to return to the clinic and to bring the diary and machine with you. At the clinic your relative/friend will have 3 fingerstick tests done. You will do the first test on your relative/friend using your machine. The research staff will do the second test using your machine and the third using the clinic’s machine, then compare the results from the 3 tests. The results from the fingerstick tests will also be compared to those from the laboratory analysis of your relative’s/friend’s blood samples. The research staff will collect the diary, download information from the machine, and give you a new diary (to write down future test results) and additional supplies. It is important for the safety of your relative/friend that you follow the prescribed schedule when doing the tests at home and report the results accurately.

**Note that you and your relative/friend must not change his/her warfarin (Coumadin) dose on your own at any time during this study.**

If your relative/friend’s test results are outside the range assigned by their doctor, you should contact the study staff for advice.

If assigned to home testing, your relative/friend may be asked to return the home testing meter at the conclusion of your participation in the study under certain conditions (for example, if the Site Investigator or your doctor feels that continued use of the meter is not in your relative/friend’s best interests).

**Patient’s Initials**
3. Risks and Discomforts:
When performing the fingerstick tests, you will be exposed to the blood of your relative/friend. This puts you at risk for catching a disease that might be carried by the blood. You will be taught ways to protect yourself from possible diseases while doing the test, such as washing your hands and wearing gloves. Because of the way the fingerstick tool is made, it would be very hard to accidentally stick yourself. If this does happen, you should wash the cut with soap and water. There may be slight bruising around the cut for a day or two.
For your relative/friend, this study includes only standard procedures used to monitor warfarin treatment: fingerstick blood samples and laboratory blood drawing. A fingerstick may cause some pain and if not done correctly may cause infection. Laboratory blood drawing (using a needle in a vein) may cause pain and minor bruising around where the needle is inserted and dizziness once your relative/friend stands up after the blood is drawn. While it is hard to predict every possible risk from being in this study, it is unlikely that there will be any serious problems since the study has no experimental procedures.

4. Potential Benefits:
You and your relative/friend may not receive any direct benefits from being in this study other than the training that you will receive. Your relative/friend may benefit if this study leads to better ways to monitor anticoagulation.

5. Other Treatment Available:
This study includes both standard procedures used to monitor warfarin treatment (fingerstick blood samples and laboratory blood drawing); there are no other accepted methods. Your relative/friend will receive his/her current health care and anticoagulation monitoring if you decide not to take part in this study.

6. Study Follow-up and Special Circumstances:
There is no follow-up nor special circumstances related to this study.

7. Withdrawal from the Study:
Your participation in this research is voluntary. You do not have to take part in this study and you may quit at any time by telling a member of the study staff. Your decision not to participate or to withdraw will have no effect on your rights to any benefits to which you are entitled or those of your relative/friend.
Research staff may end your study participation at any time if they feel it is in the best interests of your relative/friend or if you do not follow the study procedures.

______________________________
Patient’s Initials
Subject Name: ______________________________ Date: ______________

Title of Study: The Home INR Study – Part 2 - Caregiver

Principal Investigator: ____________________________ VAMC: __________

8. Confidentiality And Use of Research Results:

Participation in this study will be kept confidential. Neither your name, initials, nor other identifying data will be released or published without your permission unless we are required to do so by law. Data entered into a computer will be stored using a study patient identification code that does not identify you or your relative/friend by name, and only selected researchers associated with the study will have access to this information.

We will link the Social Security Number (SSN) of your relative/friend with his/her study patient identification code to get information on use of VA health care services. However, the list with the SSN and all data collection forms will be kept in a secure place. If the results of this study are reported in a medical journal or at meetings, you and your relative/friend will not be identified by name or by any other means.

In addition to collecting information from your relative/friend and his/her medical record, we will obtain data from centralized VA databases. These are electronic versions of selected information in these medical records, including data on all VA health care services your relative/friend received at this or other VA facilities. These electronic databases will be our primary source of information for use of all health care services for the economic analysis. We will also use the electronic data to collect information on the VA’s distribution to your relative/friend of prescription medications.

9. Special Information:

a. There will be no cost to you or your relative/friend for any of the treatment or testing done as a part of this research study.

b. Eligibility for medical care is based on the usual VA eligibility policy and is not affected by participation in a research study.

c. In the event of bad effects or physical injury resulting from participation in this study, you will get emergency medical treatment. If you believe that you received an injury from participation in this research study, you should contact Dr. ____________, the physician and Site investigator of the study, by calling ____________.

If you are an eligible veteran, you are entitled to medical care and treatment in accordance with federal law. If you are a non-eligible veteran, you can receive medical care and treatment from the VA for injury resulting from participation in this study unless the injury is due to the you not following the study procedures.

Further information about compensation may be obtained from the Medical Administration Service at the __________ VA Medical Center.

Patient’s Initials
Subject Name: ______________________________ Date: ________________

Title of Study: The Home INR Study – Part 2

Principal Investigator: __________________________ VAMC: __________

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d. If you have any questions about your rights or those of your relative/friend, you may contact the Administrative Officer of the Research Service at ____________.
e. You will be told about any significant new findings that could affect your willingness or that of your relative/friend to participate or continue to participate in this study.
f. If you decide to participate, please sign the last page of this form indicating that you understand the risks, benefits and purpose of this study

Patient's Initials

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PRIVILEGED AND CONFIDENTIAL:5/18/2006; 97
Subject Name: ____________________________ Date: ______________

Title of Study: The Home INR Study – Part 2 - Caregiver

Principal Investigator: ____________________________ VAMC: ____________________________

RESEARCH PATIENTS’ RIGHTS:

I have read or have had read to me all of the above. Dr. ____________________________ has explained the research study to me and answered all of my questions. I have been told of the risks or discomforts and possible benefits of the research study. I have been told of other choices of treatment available to me.

I understand that I do not have to take part in this research study, and my refusal to participate will involve no penalty or loss of rights to which I am entitled. I may withdraw from this research study at any time, and if I am a Veteran, I may do so without penalty or loss of VA or other benefits to which I am entitled.

The results of this research study may be published, however, I will not be identified by name or other personal identifiers. Further, my records will not be revealed unless required by law.

In case there are medical problems or questions, I have been told I can call:
Dr. ____________________________ at ____________________________ during the day, and
Dr. ____________________________ at ____________________________ after hours.

If any medical problems occur in connection with this research study the VA will provide emergency care.

I understand my rights as a research patient, and I voluntarily consent to participate in this research study. I understand what the research study is about and how and why it is being done. I will receive a signed copy of this consent form.

Caregiver’s Signature ____________________________ Date ______________

Signature of Witness ____________________________ Witness (print)

Signature of Investigator ____________________________ Date ______________

Signature of Person Obtaining Consent ____________________________ Date ______________

Signature of Investigator ____________________________ Date ______________

IF MORE THAN ONE PAGE IS USED, EACH PAGE (VAF 10-1086A) MUST BE CONSECUTIVELY NUMBERED AND SIGNED.

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Addendum to the Consent Form

When you were asked to participate in Part 2 of the THINRS study, you were told that you would be informed of any new information that may affect your willingness to continue participating in this study. The following information may affect your willingness to participate.

When Part 2 of the THINRS study started in 2003, it was scheduled to be completed in three years, through the end of August 2006, with one year to enroll and a minimum of two years of follow-up for all subjects. So, the length of your study participation was to last no more than three years. Since then the recruitment period for THINRS was extended through May 31, 2006 so that a sufficient number of subjects could be enrolled to meet the goals of the study. With a minimum two years of follow-up for all enrolled subjects, this means that THINRS study will end May 31, 2008 with the subject closeout visit taking place during the final 3 months. (The closeout visit will correspond to your final quarterly follow-up visit between March 1 and May 31, 2008.)

So, if your participation in Part 2 of THINRS started before May 31, 2005 and you want to be followed in THINRS for longer than three years, you must make your wishes known by signing this form.

Your signature on the following page indicates that you agree to be followed in this research study for more than three years.
Subject Name: ___________________________ Date: _____________

Title of Study: The Home INR Study – Part 2 Addendum

Principal Investigator: ___________________________ VAMC: ______________

RESEARCH PATIENTS’ RIGHTS:

I have read or have had read to me all of the above. Dr. _________________________ has explained the research study to me and answered all of my questions. I have been told of the risks or discomforts and possible benefits of the research study. I have been told of other choices of treatment available to me.

I authorize the use of my blood without payment for this study.

I understand that I do not have to take part in this research study, and my refusal to participate will involve no penalty or loss of rights to which I am entitled. I may withdraw from this research study at any time, and if I am a Veteran, I may do so without penalty or loss of VA or other benefits to which I am entitled.

The results of this research study may be published, however, I will not be identified by name or other personal identifiers. Further, my records will not be revealed unless required by law.

In case there are medical problems or questions, I have been told I can call:

Dr. ___________________________ at ___________________________ during the day, and

Dr. ___________________________ at ___________________________ after hours.

If any medical problems occur in connection with this research study the VA will provide emergency care.

I understand my rights as a research patient, and I voluntarily consent to participate in this research study. I understand what the research study is about and how and why it is being done. I will receive a signed copy of this consent form.

______________________________ ______________________
Patient’s Signature Date

______________________________ Witness (print)
Signature of Witness

______________________________ Date
Signature of Investigator

______________________________ Date
Signature of Person Obtaining Consent

______________________________ Date
Signature of Investigator

______________________________ Date
Signature of Investigator
When you were asked to participate in Part 2 of the THINRS study, you were told that you would be informed of any new information that may affect your willingness to continue participating in this study. The following information may affect your willingness to participate.

When Part 2 of the THINRS study started in 2003, it was scheduled to be completed in three years, through the end of August 2006, with one year to enroll and a minimum of two years of follow-up for all subjects. So, the length of your study participation was to last no more than three years. Since then the recruitment period for THINRS was extended through May 31, 2006 so that a sufficient number of subjects could be enrolled to meet the goals of the study. With a minimum two years of follow-up for all enrolled subjects, this means that THINRS study will end May 31, 2008 with the subject closeout visit taking place during the final 3 months. (The closeout visit will correspond to your relative/friend’s final quarterly follow-up visit between March 1 and May 31, 2008.)

So, if your participation in Part 2 of THINRS started before May 31, 2005 and you want to participate in THINRS for longer than three years, you must make your wishes known by signing this form.

Your signature on the following page indicates that you agree to participate in this research study for more than three years.
Subject Name: ___________________________ Date: ______________

Caregiver Name: ___________________________

Title of Study: The Home INR Study – Part 2 Addendum - Caregiver

Principal Investigator: ___________________________ VAMC: __________

RESEARCH PATIENTS’ RIGHTS:

I have read or have had read to me all of the above. Dr. ___________________________ has explained the research study to me and answered all of my questions. I have been told of the risks or discomforts and possible benefits of the research study. I have been told of other choices of treatment available to me.

I understand that I do not have to take part in this research study, and my refusal to participate will involve no penalty or loss of rights to which I am entitled. I may withdraw from this research study at any time, and if I am a Veteran, I may do so without penalty or loss of VA or other benefits to which I am entitled.

The results of this research study may be published, however, I will not be identified by name or other personal identifiers. Further, my records will not be revealed unless required by law.

In case there are medical problems or questions, I have been told I can call:

Dr. ___________________________ at ___________________________ during the day, and
Dr. ___________________________ at ___________________________ after hours.

If any medical problems occur in connection with this research study the VA will provide emergency care.

I understand my rights as a research patient, and I voluntarily consent to participate in this research study. I understand what the research study is about and how and why it is being done. I will receive a signed copy of this consent form.

______________________________ ___________________
Caregiver’s Signature Date

Signature of Witness Witness (print)

_______________________________ ___________________________________
Signature of Person Obtaining Consent Witness (print) Date

______________________________ ___________________
Signature of Investigator Date
E. HIPAA Authorization for Patient

The Federal Health Insurance Portability and Accountability Act (HIPAA) requires your health care provider to keep track of the uses of your “protected health information.” By signing this document, you are authorizing your health care provider to release your protected health information to members of the research team. During this research study some of your personal information, including health information, will be collected by VA Research personnel, and used for the scientific goals of the research study. You may be contacted in the future and be asked if you will allow your information to be used for other research studies.

The information that will be collected includes your name and social security number, which may be used to obtain information about you and your healthcare use from VA records and from non-VA medical institutions. The health information that will be collected also includes blood tests, INR results, as well as an ECG. Contact information, demographic information, medical history, warfarin history and medication history will be collected as well as assessments of numeracy, literacy, mental status and manual dexterity. You will be asked about your experiences with anti-clot treatment as well as any medical visits that occurred between study visits.

Your medical records will be reviewed once for Part 1 of the study and then periodically should you continue into Part 2 of the study. Your records will be reviewed for appointment dates, INR values, hospitalizations, test results, diagnoses and prescribed medications.

The information collected for this study will be kept confidential as required by law. Any reports or publications resulting from this study will not include any information that could identify you.

It will be necessary to send your health information, including your name and social security number, to the Palo Alto Cooperative Studies Program Coordinating Center who is sponsoring this research.

Your health information may be reviewed by authorized VA personnel, local Institutional Review Boards and other Federal agencies, such as the FDA to meet VA
and other Federal or local regulations. Your information could be redisclosed if the recipients described above are not required by law to protect the privacy of the information.

During the research study, you will not be able to have access to the research data that is collected about you until after the study is completed and the study results have been determined or published. After the study is completed you may request your health information.

This authorizes this hospital and the Palo Alto Cooperative Studies Program Coordinating Center to use your personal health information indefinitely. [NOTE TO SITES: If per local regulations, this is not true of your site, insert appropriate expiration] You do have the right at any time to take back your permission to use your personal health information for research purposes. However, if your information has already been combined with other peoples' information in the study, such as when numbers are averaged, or if it has been sent to the Cooperative Studies Program Coordinating Center, they will continue to use it but no further information about you will be used. When your information is combined with other peoples' information in the study, your personal information cannot be identified.

If you have questions concerning taking back your permission, you may contact _______________ at _____________. To take back your permission for use of your personal information you notify contact Dr. _____________ in writing at _________________. Your participation in this research study will end when you take back your permission or do not give your permission. However, you will still receive all the medical care and benefits for which you are otherwise eligible.

__________________________  ______________________
Patient or legal representative signature    Date

If signed by legal representative, relationship to patient

____________________________________________________________

____________________       _______________
Signature of Witness       Date

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F. HIPAA Authorization for Caregiver

By signing this document, you are authorizing your health care provider to release your protected health information to members of the research team. During this research study some of your personal information will be collected by VA Research personnel, and may be used for the scientific goals of the research study.

The information that will be collected includes your name and demographic information. Assessments of numeracy, literacy, mental status and manual dexterity will also be collected.

The information collected for this study will be kept confidential as required by law. Any reports or publications resulting from this study will not include any information that could identify you.

It will be necessary to send your information to the Palo Alto Cooperative Studies Program Coordinating Center who is sponsoring this research.

Your records may be reviewed by authorized VA personnel, local Institutional Review Boards and other Federal agencies, such as the FDA to meet VA and other Federal or local regulations. Your information could be redisclosed if the recipients described above are not required by law to protect the privacy of the information.

During the research study, you will not be able to have access to the research data that is collected about you until after the study is completed and the study results have been determined or published. After the study is completed you may request your information.

This authorizes this hospital and the Palo Alto Cooperative Studies Program Coordinating Center to use your personal health information indefinitely. [NOTE TO SITES: If per local regulations, this is not true of your site, insert appropriate expiration]

You do have the right at any time to take back your permission to use your personal information for research purposes. However, if your information has already been combined with other peoples' information in the study, such as when numbers are averaged, or if it has been sent to the Cooperative Studies Program Coordinating Center, they will continue to use it but no further information about you will be used.
When your information is combined with other peoples’ information in the study, your personal information cannot be identified.

If you have questions concerning taking back your permission, you may contact ______________ at ______________. To take back your permission for use of your personal information you must notify Dr. ______________ in writing at _________________. Your participation in this research study will end when you take back your permission or do not give your permission. However, you will still receive all the medical care and benefits for which you are otherwise eligible.

_________________________________   _________________
Patient or legal representative signature    Date

If signed by legal representative, relationship to patient

____________________________________________________________

_________________       ________________
Signature of Witness       Date

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G. Minutes of the Human Rights Committee Meeting

The Human Rights Committee met on January 5, 2000 and unanimously approved CSP #481. The HRC also met on October 3, 2002 to review changes made to the protocol and informed consents. The minutes from both meetings follow.
IX. REFERENCES


Gray HW, Bessent RG. Pulmonary embolism exclusion: a practical approach to low probability using the PIOPED data. Prospective Investigation of Pulmonary
Harrell F.E. Jr.: Predicting Outcomes: Applied Survival Analysis and Logistic Regression. School of Medicine, University of Virginia, 1996.
National Cancer Institute. Common Toxicity Criteria, version 2.0
Peterson B, George S.L.: Sample size requirements and length of study for testing interaction in a 2 x k factorial design when time-to-failure is the outcome. Controlled Clinical Trials 14:511-522, 1993.


X. BUDGET AND BUDGET JUSTIFICATION

A. General Overview and Study Duration

The study budget will cover 47 months (see Table 7 below) including 13 months of screening and enrollment and two years of follow-up.

Salaries are based on the January 2002 rates using local geographical figures for staff at the Co-Chairs’ offices, the CSPCC, and the CSP Research Pharmacy Coordinating Center. Participating sites have not been identified, so we used the Chicago locality rates to estimate their salary needs. We also used a 5% rate for yearly salary increases and assumed a 30% rate for personnel benefits.

Note that the budget shows no costs for lab work. Since the study does not require analyses over and above that provided as part of a warfarin patient’s usual care (quarterly CBC and INR checks), the labs at the participating sites will bear these costs as part of their standard operating procedures.

Since funding for travel related to the study (e.g., annual Executive Committee Study Group meetings, and DSMB) is paid by CSP Central Office, vendor certification performed by the Albuquerque CSPCRPCC is the only travel included in the budget.

Table 7: Study Duration

<table>
<thead>
<tr>
<th>Phase</th>
<th>Month</th>
</tr>
</thead>
<tbody>
<tr>
<td>Startup at Chairs’ offices, CSPCC</td>
<td>1-4</td>
</tr>
<tr>
<td>Startup at sites</td>
<td>3-4</td>
</tr>
<tr>
<td>screening and conducting Part 1</td>
<td>5-16</td>
</tr>
<tr>
<td>enrollment into Part 2</td>
<td>6-17</td>
</tr>
<tr>
<td>follow-up (if enrolled in month 17, follow-up ends month 41)</td>
<td>6-41</td>
</tr>
<tr>
<td>closeout for sites</td>
<td>42</td>
</tr>
<tr>
<td>Closeout for Chairs’ offices and CSPCC</td>
<td>42-47</td>
</tr>
</tbody>
</table>
B. Chairs’ Office: Durham

1. Personnel

Research Coordinator (GS-9 step 1, 1.0 FTE): This staff member will triage all study questions from the study staff at the sites, CSPCC, and CSP Pharmacy. The Research Coordinator will deal with issues related to the research design, be responsible for monitoring study progress, facilitate communications between sites, and work closely with the Loma Linda Clinical Coordinator to assure that ACS and INR monitor questions are addressed promptly and accurately.

2. Other Operating Costs

These include a desktop computer and related software, a printer, and supply money.

3. Endpoints Committee

We estimate 195 endpoints will be reviewed over the course of the study. 20% during Year 1, 30% during Year 2, and 50% during Year 3. The review of the endpoints will be conducted by the Clinical Events Committee located at Duke University. This includes a per review charge for the Committee as well as a per review charge for Internal Reviewers.

C. Chairs’ Office: Loma Linda

1. Personnel

Clinical Coordinator (GS-9 step 1, 1.0 FTE): This person will be responsible for overseeing clinical aspects of the project. Specific duties include verifying that the operations of the ACS’s are in accord with the functional specifications defined by the protocol, training site staff on the use of the INR monitors, communicating with manufacturers regarding meter issues, and answering questions from sites related to clinical operations of the ACS and or the INR monitors.

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2. Other Operating Costs

These include a desktop computer and related software, a printer, and supply money.

D. Participating Centers

1. Personnel

Study Coordinator or SC (GS-9 step 3, 0.5 FTE): This person will screen and help enroll patients, collect data (on the case report forms, download data from the meters if at a substudy site), schedule study visits to the AC clinic, help train PST patients in the use of the monitors, provide clerical support to the SI, and serve as the backup for the AC Manager.

Anticoagulation (AC) Manager (GS-9 step 3, 0.5 FTE): This staff member will monitor the AC status of each study patient and serve as the backup for the SC.

2. Other Operating Costs

Money is included for miscellaneous office supplies.

3. Substudy bonus payment

Six sites will participate in the substudy. Due to the added administrative burden, the site will receive a $100 bonus payment for each patient which will be allocated as follows: $50 at randomization, $25 at follow-up visit 4 and $25 at follow-up visit 6. A max of 400 patients (from 6 sites) will be randomized to the substudy.

E. CSPCC Beyond Core Costs

1. Personnel

Statistical Programmer (for cost and utilization data), Level 1, 0.5 FTE: This person will download data from VA utilization files and use this with data downloaded by the Economic Research Health Science Specialist from the local DHCP’s and

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information on non-VA health care to produce reports and conduct final analyses for cost and utilization of health care.

RHSS (for cost and utilization data), GS-9 step 1, 0.5 FTE: This person downloads data from local the DHCP’s and helps the Statistical Programmer maintain and verify cost and utilization databases.

2. Other operating costs, main study

a. The study will require 2 interviewer-administered Health Utilities Index questionnaires (i.e., self and proxy versions). The HUI measure includes a health-status classification system and a preference-based scoring system. The licensing fee is $4500 for use of the 2 interviewer-administered questionnaires and matching coding/procedure manual.

b. Money is included to purchase a computer, software, printer and fax machine for each of the 32 sites.

c. Each screened patient will receive a diary in Part 1 and each enrolled patient will need 8 diaries to complete Part 2. At an estimated unit cost of $3, the 25,600 diaries will cost $76,800.

d. We estimate we will need 1920 monitors at approximately $1000 each. The 320 over and above the 1600 PST patients represents a 20 percent surplus that will be needed to conduct Part 1 of the study (in which everyone screened receives a monitor) and in case of meter malfunction. The total cost is $1.92 million.

e. We estimate the cuvettes will cost $110 per box of 25. For each patient we estimate we will need 12 to 18 strips to complete Part 1 (2 for training purposes, 4 to 8 for twice a week home testing, 4 to 6 for tests at the clinic, and 2 in case tests must be repeated). Assuming all PST patients test once a week in Part 2 for an average length of 2.5 years, each PST patient will require 250 strips (130 for weekly home testing, 30
for quarterly clinic visits, and 90 or 3 per month to monitor out-of-range values and to repeat tests as needed). If we assume 20 percent of those screened are ineligible (i.e., 4000 screened to enroll 3200), the number of strips needed for Part 1 is 48,000 to 64,000. The number needed for Part 2 if the average length of testing is 2.5 years is 400,000 (average of 250 per PST patient). Under the conservative assumption that only 448,000 are needed for Parts 1 and 2, the cost is $1,971,200.

3. Other Operating Costs, Substudy

To do the Part 2 Substudy, 100 PST patients will do twice a week home testing and 100 will home test once every four weeks. The twice a week group needs 470 strips per person (260 at home, 30 in clinic, and 180 or 6 per month for out-of-range monitoring and in case repeat testing is needed). Each patient in the group that tests every 4 weeks needs 123 strips (33 at home, 30 in clinic, and 60 or about 2 per test period for out-of-range monitoring and in case repeat testing is needed). The average for these 200 patients is 297 or about 47 more than the average for patients who test weekly. Thus, the Substudy requires about 9,250 additional strips at a cost of $40,700.

F. CSP Research Pharmacy Coordinating Center Beyond Core Costs

1. Personnel

Pharmaceutical Project Manager, GS-11/5, 0.25 FTE: The Pharmaceutical Project Manager (PPM) acts as the Assistant Director's liaison to study personnel at participating sites, the Cooperative Studies Program (CSP) Coordinating Centers or non-CSP Coordinating Centers, and the Study Chairperson(s)'s Office, involving matters not requiring clinical judgment. Under the direction of the Clinical Research Pharmacist/Assistant Center Director (ACD), the PPM performs the following tasks during the course a study: coordinates project activities within the Center, monitors adherence to project deadlines, and communicates with Center employees on behalf of the ACD; performs assigned tasks involved in planning a study, including literature searches, and identifies sources of specific products, supplies, and equipment when required; monitors the receipt of required study data from participating sites and...
statistical centers; reviews data and directs processing of data; investigates conflicting
information; monitors levels of study product at participating sites; reviews and initiates
production requests for shipments as appropriate; ensures that all shipments are made
in a timely and accurate manner; evaluates the need to assign emergency study
product at sites; makes and records such assignments when necessary; monitors
expiration dating of study products; initiates and monitors the retrieval/recall of study
product from participating sites; analyzes and monitors the requirements for study
products, and arranges for the acquisition of study products and other study related
supplies; prepares various study-related reports and summaries for use within Center
and VA CSP, both for routine and non-routine purposes; formulates the study budget;
conducts a periodic budget review for each assigned study, revising the budget as
necessary; tracks funds received and disbursed for each study, if required; coordinates
domestic and international shipping contracts, if appropriate, and resolves any shipping
or customs problems; assesses and supplements, as necessary, the Center's inventory
tracking software (DIIS) to meet specific needs of assigned studies; advises the
Information Technology Section (ITS) and/or the PM regarding software and hardware
requirements to achieve study and Center objectives; and travels to study group
meetings and participates in the presentation of Center study related issues, when
required.

Internet Specialist, GS-9/5, 0.5 FTE: This person will establish and maintain the
Internet web site used to create and maintain database of information which PST
patients enter by phone. He/she also answers questions that the patients have about
the automated telephone system.

2. Other Operating Costs

This includes costs for software to develop the web site, one 1-800 phone line
(for patients to enter data) and telephone system upgrade, a computer to support the
Internet web site which will make available study documentation including patient INR
data to allow the sites to monitor patient (e.g., reports on INR values, out-of-range
value, etc), as well as shipping costs, miscellaneous supplies (e.g. Patient ID cards),
and travel for vendor certification. We estimate a total of 400,000 calls will be needed
over the course of the study. Each call is believed to be 2 minutes in length. 800,000
minutes of calls at a rate of 7 cents per minute plus a monthly fee of $10, for a total of $56,360.

G. Capitation

It is anticipated that there will be 32 participating sites involved in this study, with each site enrolling about 100 patients. This is a capitated study and sites will be reimbursed up to $2000 per subject which will be allocated as follows: $500 at randomization and $150 at each follow-up visit. A site that randomizes and follows its target of 100 patients will be reimbursed a total of $200,000, which matches the model site budget. To start up a site, it will be advanced $40,000 upon completion of R&D approval. As soon as the site has reached a reimbursement level greater than $40,000 (as a result of study activity) the further reimbursements will be based on the capitation rates above. Sites may enroll over target.

H. Itemized Budget

The projected study budget is as follows.
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<th>Summary</th>
<th>March-FY02</th>
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<th>FY 04</th>
<th>FY 05</th>
<th>FY 06</th>
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<td>FU Yr 1</td>
<td>FU Yr 2</td>
<td>Closeout</td>
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<th>FY 04</th>
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<td>Enroll</td>
<td>FU Yr 1</td>
<td>FU Yr 2</td>
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PRIVILEGED AND CONFIDENTIAL;5/18/2006; 127
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<td>FU Yr 2</td>
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| TOTAL                                   | 973,103| 3,263,340| 123,711| 129,897|

TOTAL: 4,528,792
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<td>3,033</td>
<td>15,290</td>
<td>16,050</td>
<td>16,361</td>
<td>4,215</td>
</tr>
<tr>
<td>Research Assistant</td>
<td>10%</td>
<td>35,175</td>
<td>529</td>
<td>3,316</td>
<td>3,438</td>
<td>3,058</td>
<td>914</td>
</tr>
<tr>
<td>PI's Named Associate</td>
<td>5%</td>
<td>40,938</td>
<td>10,544</td>
<td>40,938</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>PI's Senior Associate</td>
<td>5%</td>
<td>40,938</td>
<td>10,544</td>
<td>40,938</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>PI's Lab Special</td>
<td>5%</td>
<td>40,938</td>
<td>10,544</td>
<td>40,938</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Investigator Co-PI</td>
<td>5%</td>
<td>40,938</td>
<td>10,544</td>
<td>40,938</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>UC-Medical Co-PI</td>
<td>5%</td>
<td>40,938</td>
<td>10,544</td>
<td>40,938</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Subtotal</td>
<td></td>
<td>16,132</td>
<td>6,537</td>
<td>68,903</td>
<td>72,344</td>
<td>50,041</td>
<td>9,561</td>
</tr>
<tr>
<td>Fringe</td>
<td></td>
<td>2,023</td>
<td>20,095</td>
<td>9,200</td>
<td>9,435</td>
<td>2,624</td>
<td>53,891</td>
</tr>
<tr>
<td>Core-funded Labor</td>
<td></td>
<td>18,155</td>
<td>86,632</td>
<td>78,103</td>
<td>80,969</td>
<td>52,665</td>
<td>12,185</td>
</tr>
</tbody>
</table>

BEYOND CORE COSTS

PERSONNEL

Pharmaceutical Project Manager: 25% | 40,192 | 8,138 | 26,951 | 26,779 | 27,977 | 37,974 | 22,439 |
Development & Customer Support: 25% | 40,192 | 8,138 | 26,951 | 26,779 | 27,977 | 37,974 | 22,439 |
Subtotal                          | 16,352 | 16,467 | 53,802 | 54,558 | 55,954 | 75,458 | 45,476 |
Fringe                             | 4,616 | 16,467 | 53,802 | 54,558 | 55,954 | 75,458 | 45,476 |
Total Labor                       | 21,026 | 56,935 | 107,604 | 110,116 | 111,908 | 150,915 | 90,952 |

STUDY AGENTS - see assumptions

Designers                           | -      | -     | -     | -     | -     | -     | -     |
Test Strips                        | -      | -     | -     | -     | -     | -     | -     |
Licensing and ars & services       | -      | -     | -     | -     | -     | -     | -     |
Camping & Care                     | -      | -     | -     | -     | -     | -     | -     |
Total Study Agents                 | -      | -     | -     | -     | -     | -     | -     |

SUPPLIES

Patient ID Cards ($25 per 100) | 6,000  | 0.00  | 150   | -     | -     | -     | 150   |
Medical Supplies                  | 1,000  | 550   | 525   | 591   | -     | -     | 2,576 |
Total Supplies                    | 1,150  | 500   | 525   | 591   | -     | -     | 2,726 |

EQUIPMENT

Telephone System Upgrade            | 5,000  | -     | -     | -     | -     | -     | 5,000  |
Computer Web Site Development      | 2,000  | -     | -     | -     | -     | -     | 2,000  |
Software Web Site Development      | 2,000  | -     | -     | -     | -     | -     | 2,000  |
Total Equipment                    | 10,000 | -     | -     | -     | -     | -     | 10,000 |

PACKAGING & SHIPPING

FEDEX & insuring materials       | 44,916 | 62,714 | 65,409 | 12,464 | -     | -     | 106,684 |
Total Packaging and Shipping     | 44,916 | 62,714 | 65,409 | 12,464 | -     | -     | 106,684 |

TRAVEL

Vendor Certificates                | 7,000  | 2,000  | -     | -     | -     | -     | 2,000  |
Total Travel                      | 2,000  | -     | -     | -     | -     | -     | 2,000  |

1000 Phone Calls

Phone calls                       | 400,000 | 0.00  | 10,767 | 10,767 | 10,767 | -     | 50,266 |
Total Phone calls                  | 10,767  | 10,767 | 10,767 | 10,767 | -     | -     | 50,266 |

TOTALS

CORE ENDED                        | 75,465 | 105,634 | 37,650 | 10,634 | 9,098 | 231,026 |
BEYOND CORE                       | 78,321 | 197,168 | 57,565 | 126,569 | 22,476 | 671,562 |
TOTAL STUDY                       | 115,786 | 272,802 | 95,215 | 147,203 | 31,974 | 902,588 |

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<table>
<thead>
<tr>
<th>Line Item</th>
<th>Quantity</th>
<th>Unit</th>
<th>Start-Up</th>
<th>Year 1</th>
<th>Year 2</th>
<th>Year 3</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ASSUMPTIONS:</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inflation</td>
<td>5%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fringe</td>
<td>30%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of Total Patients</td>
<td></td>
<td></td>
<td></td>
<td>3,200</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Number of Patients Receiving Devices</td>
<td></td>
<td></td>
<td></td>
<td>1,600</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of Devices (1,600 +20% to conduct Part 1 and in case of device failure)</td>
<td>1,920</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of Cuvettes (does include cuvettes for Sub-study)</td>
<td>457,250</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of Boxes of Cuvettes @ 25 cuvettes per box</td>
<td>18,290</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of VA Sites</td>
<td></td>
<td></td>
<td></td>
<td>32</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Recruitment = 1 year</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Follow-up = 2 - 3 years</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total Length of Study = 3 years</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Close Out = 3 Mos for FDAR</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Core Funding is NOT being requested, is only included for completeness
* Study devices, cuvettes/strips, lancing tool and lancets, and carrying cases - To be purchased by Palo Alto for distribution by Albuquerque to study sites
* Beyond Core Labor = PPM and ITS internet specialist responsible for establishing and maintaining the Web Site and answering patients' questions regarding the automated telephone system.
* Software is needed to develop and maintain the web site.
* Computer equipment is needed for the phone system which subjects in the home-testing arm will use to relay study data to the central server, and for the Internet which will be used to relay patient data back to the study sites to allow site study staff to monitor patients in the home-testing study arm
* FEDEX and shipping materials includes all costs related to the processing and shipping of study agents. For this calculation the assumption is made that the shipment of cuvettes/strips will be in cold packs as is required for one potential Device Vendor’s cuvettes/strips; therefore, shipping material costs could decrease if this Device Vendor is not selected.
* No devices or cuvettes/strips will need to be destroyed.
XI. CURRICULUM VITAE

David Matchar, M.D., Co-Chair
Alan Jacobson, M.D., Co-Chair
Robert Edson, M.A., Biostatistician
Ciaran Phibbs, Ph.D., Health Economist
DATE: October 1, 1999

Name: David B. Matchar, M.D., FACP

Primary academic appointment: Department of Medicine

Secondary appointment: Center for Clinical Health Policy Research

Social Security number: 216-48-3910

Present academic rank and title: Professor and Director, Center for Clinical Health Policy Research

Date and rank of first Duke faculty appointment: 1985, Associate in Medicine

Medical licensure (National Boards, State):

1980 Maryland State Board of Medical Examiners
1983 North Carolina Board of Medical Examiners

Specialty certification and dates: 1984 Diplomat in Internal Medicine

Date of birth: 9/29/55  
Place: Baltimore, MD

Citizen of: USA

Education:

<table>
<thead>
<tr>
<th>School</th>
<th>Place</th>
<th>Date</th>
<th>Degree</th>
</tr>
</thead>
<tbody>
<tr>
<td>High School</td>
<td>Pikesville Sr. High</td>
<td>1972</td>
<td></td>
</tr>
<tr>
<td>College</td>
<td>Princeton University</td>
<td>1976</td>
<td>A.B</td>
</tr>
<tr>
<td>Graduate or</td>
<td>University of Maryland</td>
<td>1980</td>
<td>MD</td>
</tr>
<tr>
<td>Professional School</td>
<td>Harvard School of Public Health</td>
<td>1983</td>
<td></td>
</tr>
</tbody>
</table>

Positions and Honors:

1999 - Professor, Division of General Internal Medicine, Department of Medicine, Duke University Medical Center, Durham, NC

1993 - 1999 Associate Professor, Division of General Internal Medicine, Department of Medicine, Duke University Medical Center, Durham, NC

1989 - Adjunct Professor, Department of Health Policy and Administration, School of Public Health, University of North Carolina, Chapel Hill, NC

1988 - Director, Center for Clinical Health Policy Research Duke University, Durham, NC

1987 – 1993 Assistant Professor, Division of General Internal Medicine, Department of Medicine, Duke University Medical Center, Durham, NC
1985-1989  Medical Director, Hospital Based Home Care Program, VA Medical Center, Durham, NC
1985-   Research Associate, Health Services Research Field Program, VA Medical Center, Durham, NC
1984   Ciba-Corning Medical Training Fellowship in Medical Decision Sciences
1980-   Alpha Omega Alpha Medical Honor Society
1980   Cum Laude, University of Maryland School of Medicine
1977   Assistant Statistician, Center for Disease Control, Atlanta, GA
1975-76  Statistician, Center for Environmental Studies, Princeton, NJ

PUBLICATIONS: (64 of 112 publications)


In Press


In Review
63. Barber MD, Myers ER, MATCHAR DB. Physician decision making in the management of uterine fibroids: variability in estimates of key probabilities. In review.

64. Kulasingam SL, Samsa S, Zarin DA, et al. When should functional neuroimaging techniques be used in the diagnosis and management of Alzheimer’s disease and dementia? In review

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CURRICULUM VITAE
Alan Kenneth Jacobson, M.D., F.A.C.C.
October 2002

Business Address:             Jerry L. Pettis VA Medical Center
                             Cardiology Section (111C)
                             11201 Benton Street
                             Loma Linda, CA 92357

Business Phone   (909) 422-3097
                             FAX (909)-777-3273

Home Address:       11696 Largo Court
                             Loma Linda, CA 92354

Date of Birth:      August 26, 1955

Place of Birth:     Burnaby, British Columbia, CANADA

Citizenship:        Canadian/United States

Social Security Number:    S.S.# 532-64-1282

EDUCATION:
Walla Walla College       B. Sc.   1977
College Place, Washington

Loma Linda University School of Medicine   M.D.   1981
Loma Linda, California

MEDICAL TRAINING:
Internship:
    Loma Linda University Medical Center
       (Affiliated Hospitals)
    Straight Internal Medicine Internship  1981-1982

Residency:
    Loma Linda University Medical Center
       (Affiliated Hospitals)
    Internal Medicine                     1982-1984

Fellowship:
    Loma Linda University Medical Center
       (Affiliated Hospitals)
    Cardiology                            1985-1988

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PRACTICE:
Ambulatory Care Clinic 1984-1985
Jerry L. Pettis Memorial VA Medical Center
Loma Linda, California
   Staff Physician

Loma Linda Faculty Medical Group 1988-1989
28115 Bradley Road
Sun City, California
   Staff Cardiologist

Cardiology Section 1988-present
Jerry L. Pettis Memorial VA Medical Center
Loma Linda, California

Loma Linda University Cardiology Medical Group 8/90 — 9/92
Loma Linda International Heart Institute
11234 Anderson Street
P.O. Box 2000
Loma Linda California 92354-0200
   Staff Cardiologist
   Director of Treadmill Testing

Responsibilities
   Acting ACOS, Research
   Staff Cardiologist
   Director, Cardiac Pacing
   Director, Anticoagulation Clinic
   Coordinator, Cardiology Computer Services
   Member, Research & Development Committee
   Member, Human Studies Subcommittee (IRB)
   Member, End-Points Committee for VA Co-operative Study #399

Past Responsibilities
   Coordinator, Outpatient Cardiology Clinics
   Chair, Information Resource Management Advisory Committee
   Member, Clinical Executive Board, Loma Linda VAMC
   Member, Executive Council, Loma Linda VAMC
   VISN Informatics Council
   Liaison to Clinical Practice Council
   Co-Chairman, Clinical Guideline Implementation Committee
   Member, Medical Center Financial Planning Committee

HOSPITAL APPOINTMENTS:
Jerry L. Pettis Memorial VA Medical Center, Loma Linda, California

TEACHING APPOINTMENT:

PRIVILEGED AND CONFIDENTIAL;5/18/2006; 139
Assistant Professor in Internal Medicine
Department of Internal Medicine,
Loma Linda University
Loma Linda, California

LICENSURE:
California:   # G48891
DEA:   # AJ1824906
Radiography permit   # RHD 129537
Diplomate of American Board of Internal Medicine   1988
Diplomate Cardiovascular Subspeciality Board   1989
Testamur NASPE—Examination of Special Competency in Cardiac Pacing   1991

SOCIETY MEMBERSHIPS:
American College of Cardiology
American Heart Association
North American Society of Pacing and Electrophysiology
International Society on Thrombosis and Haemostasis
International Self Monitoring of Anticoagulation Association

COMMITTEE PARTICIPATION:
Loma Linda VA Medical Center IRB
Loma Linda University Medical Center IRB
Loma Linda VA Medical Center R & D Committee
CSP #341 Executive Committee
CSP #341 End Points Committee
CSP #481 Planning Committee

PROGRAM DEVELOPMENT:
Preceptorship for training in the establishment and maintenance of Anticoagulation Clinics and Antithrombotic Therapy. The preceptorship is for 2 days and attendance is from across the United States. It is held 8 times a year.

CURRENT RESEARCH ACTIVITIES:
A computerized search method for optimizing anticoagulation enrollment in atrial fibrillation.
1993 - ongoing       DuPont Pharma

Effects of Antiarrhythmic Therapy in Maintaining Stability of Sinus Rhythm in AFIB
1997-ongoing       Veterans Administration

Evaluation of Patient Self Testing for Blood Clotting (INR) Determinations utilizing the ProTime Instrument and Fingerstick Sampling
1998-ongoing       ITC

Evaluation of LifeScan coagulation Test System
Physician Directed patient Self-Testing of the Prothrombin Time with the Avocet PT
1999-ongoing
Avocet

WATCH (Warfarin and Antiplatelet Therapy Study in Patients with Congestive Heart Failure)
1999-ongoing
VA Coop Study #442

A Systematic O/P Anticoag Mgmt Services (ACS) Assess Study to Det Mgmt
1999-ongoing
HSR&D Exec Comm Stroke QUERI

Rubicon INR Monitoring system-Professional Use & Patient Self Testing Study
1999-ongoing
LifeScan (Johnson & Johnson)

HemoSense PT/INR Meter: Professional Use at the Point of Care
1999-ongoing
HemoSense

HemoSense Test System for PT/INR: Physician Directed Home Use Clinical Trial
1999-ongoing
HemoSense

HemoSense: Physician Directed Home Use Long Term Surveillance Protocol
2000-ongoing
HemoSense

HemoSense Test System for PT/INR: High INR Sample Testing Protocol
2000-ongoing
HemoSense

Tinzaparin Vs Unfractionated Heparin in Subj Who Rec L-Term Warfarin
2000-ongoing
DuPont

SPORTIF V Oral Direct Thrombin Inhibitor H376/95 Compared w/Dose Adjusted Warfarin
2000-ongoing
Zeneca

THINRS (The Home INR Study) 2001
Co-Principal Investigator
VA Coop Study #481

(ADONIS) American-Australian-African Trial with Dronedarone in Atrial Fibrillation
2002-ongoing
Sanofi-Synthelabo

Pro#EFC 3558 (APOLLO) Fondaparinux Sodium w/Intermit Pneumatic Compression VS Intermit Compression Alone
2002-ongoing
Sanofi-Synthelabo

(EXCLAIM) Extended VTE Propylaxis in Acutely Medically Ill Immobilized Patients
2002-ongoing
Aventis
(ONTARGET) Ongoing Telmisartan Alone & in Combination with Ramipril Global Endpoint Trial
2002-ongoing Aventis

(TRANSCEND) Telmisartan Randomized Assessment Study in Ace Intolerant Subjects with Cardiovascular Disease
2002-ongoing Aventis

PUBLICATIONS:


Anticoagulation in Atrial Fibrillation; A Novel Approach to Improve Translation of Clinical Trials into Practice. Makowski MT, Jacobson AK, Ferry DR, Heywood JT. Manuscript submitted to Archives of Internal Medicine.


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CURRICULUM VITAE for ROBERT G. EDSON (December 2002)

ADDRESS

VA Palo Alto Health Care System
Cooperative Studies Program Coordinating Center (151-K)
795 Willow Rd.
Bldg. 205, Room 205
Menlo Park, CA 94025-2539

TELEPHONE, FAX, AND E-MAIL INFORMATION

Phone Number: (650) 493-5000 x22250
Fax Number: (650) 617-2605
E-mail: bob.edson@med.va.gov

EDUCATION

M.A., Applied Mathematics (with Statistical Emphasis)
University of California at Santa Barbara. December 1978

B.S. with High Honors, Mathematics
University of California at Santa Barbara. June 1977

Non-degree. Sampling Theory and Variance Estimation

PROFESSIONAL EXPERIENCE

Biostatistician. Palo Alto Cooperative Studies Program Coordinating Center.
Menlo Park, CA. April 1991 to present

Presidio of San Francisco, CA. September 1989 to April 1991


January 1979 to March 1984

PROFESSIONAL SOCIETY MEMBERSHIP

American Statistical Association; Society for Clinical Trials

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PRESENTATIONS


3. Edson RG, Lavori PW, Froelicher VF, Lehmann KG, and Thomas RG for the VA Cooperative Studies Group on Computerized Exercise Electrocardiography: Application of 'Design' S Functions to Build Multivariate Models for Predicting
PRESENTATIONS WITH COLLABORATORS


COOPERATIVE STUDIES PROGRAM ACTIVITIES

Study Biostatistician

CS #016: The Diagnostic and Prognostic Value of the Computerized Exercise ECG (QUEXTA)
CS #020: Cost and Outcome of Telephone Care (TELECARE)
CS #394: Vitamin E Treatment of Tardive Dyskinesia
CS #1017: Outpatient Selegiline Treatment for Cocaine Dependence (OutSeT)
CS #481: The Home INR Study (THINRS)

Design Biostatistician on the Planning Committee

CS #001: Influence of Delivery Site and Other Factors Upon Resource Use and the Appropriateness of Dental Care
CS #006: Evaluation of GEM Units and Geriatric Follow-up
CS #012: Effectiveness of Geriatric Evaluation and Management
CS #526: DITPA, a Thyroid Analog to Treat Heart Failure: Phase II Trial

Faculty Mentor

CSP Clinical Research Methods Course, 2001-2002

OTHER ACTIVITIES

Member, VA Palo Alto Health Care System Biomedical Research Subcommittee, June 2002 to present
CURRICULUM VITAE
CIARAN S. PHIBBS, PH.D. May 2006
Health Economics Resource Center (152)
Veterans Affairs Medical Center
795 Willow Road
Menlo Park, CA 94025
(650)-493-5000 x22813 e-mail: cphibbs@odd.stanford.edu

EDUCATIONAL BACKGROUND
University of California, San Diego, Ph.D. in Economics, August, 1987.
St. Lawrence University, Canton, New York, B.A. in Economics May 1979.

RESEARCH AND PROFESSIONAL EXPERIENCE
1991-present Research Economist, Center for Health Care Evaluation, and Cooperative Studies Program, Veterans Affairs Medical Center, Palo Alto, California.
1992-present Consulting Assistant Professor, Department of Health Research and Policy, Stanford University School of Medicine, Stanford, California.
1999-present Associate Director, Health Economics Resource Center, Veterans Affairs Medical Center, Palo Alto, California.
1995, 1998 Visiting Assistant Professor, Department of Economics, Stanford University
1990-1991 Research Associate, Institute for Health Policy Studies, University of California, San Francisco.
1989-1990 Assistant Professor of Health Economics, School of Public Health, Columbia University.
1987-1989 Postdoctoral fellow in the University of California, Berkeley/University of California, San Francisco Health Services Research Training Program

BIBLIOGRAPHY
Mooney C, Zwanziger J, Phibbs CS, Schmitt S. Is Travel Distance a Barrier to Veterans' Use of VA Hospitals for Medical-Surgical Care. In press, Social Science and Medicine, 2000;50:June
Lightwood JM, Phibbs CS, Glantz SA. Short Term Health and Economic Benefits Smoking Cessation: Low Birth Weight. Pediatrics, 1999;104:1312-1320.

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papers under review
Cifuentes J, Bronstein JM, Phibbs CS, Phibbs RH, Carlo WA. Mortality According to Level of Neonatal Care at Hospital of Birth in Low Birth Weight Infants. Draft, University of Alabama, Birmingham, May 1999.

Phibbs CS, Bronstein JM, Buxton E, Phibbs RH. The effect on risk-adjusted neonatal mortality of linking discharge data to birth certificate data. Draft, Palo Alto VAMC, April 1999.


**REVIEWER FOR FUNDING AGENCIES**
Agency for Health Care Policy and Research:
Health Care Research Training Study Section, 1999-current
Special Small Grants Study Section, 1997
Special Study Section on Market Forces, 1995

**GRANTS AND CONTRACTS**
National Institute for Child Health and Human Development RO1 HD36914 ARegionalization, Market Forces, and Neonatal Mortality. Principal Investigator. 4/1/00-3/31/04, $983,112.

PRIVILEGED AND CONFIDENTIAL; 5/18/2006; 149
Department of Veterans Affairs, Health Services Research & Development SDR # ECN 99017, Health Economics Resource Center. Co-Investigator and Associate Director. 9/1/99-8/31/02, $1,050,000


Department of Veterans Affairs, Health Services Research & Development IIR #95-122.1, Factors That Influence the Demand for Outpatient VA Services. Principal Investigator. 7/1/95-8/30/99, $328,100.


Department of Veterans Affairs, Health Services Research & Development IIR #94-033.1, Predicting Inpatient Service Use Among VA Substance Abuse Patients. Co-Investigator (5% effort). 10/1/95-3/30/98, $178,000.

Agency for Health Care Policy and Research RO1-HS 06123-03, "Physiologic Severity Index for Neonatal Intensive Care." Principal Investigator, Douglas Richardson, Harvard University. Subcontract as co-investigator to conduct the economic analysis. 7/1/91-6/30/92, $18,000
XII. BIOSTATISTICAL REVIEW AND DATA PROCESSING (BRDP)

The tables in this section are examples of the type of information that will be generated during the study for periodic evaluation by the Executive Committee and the DSMB.

Tables on patient accrual will be used to monitor the progress of patient enrollment into the study, overall and by participating VAMC. Baseline characteristics will be compared by VAMC to ensure the comparability of patients across VAMC. Adverse events, terminations, and counts of data forms missing or with errors will also be compared by VAMC.

When appropriate, the data in the tables will be supplied to the DSMB by treatment group as well as overall.

Table 1. Recruitment by Hospital

<table>
<thead>
<tr>
<th>Hospital</th>
<th>No. Screened in Part 1</th>
<th>No. Randomized (%) in Part 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>...</td>
<td></td>
<td></td>
</tr>
<tr>
<td>H</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TOTAL</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 2. Balance on Stratification Variables

<table>
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<tr>
<th>Length of anticoagulation</th>
<th>Indication</th>
<th>HOSPITAL</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;3 months</td>
<td>Atrial fibrillation (AF)</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Mechanical heart value (MHV) or AF and MHV</td>
<td>2</td>
</tr>
<tr>
<td>&gt;=3 months</td>
<td>AF</td>
<td>....</td>
</tr>
<tr>
<td></td>
<td>MHV or AF and MHV</td>
<td>H</td>
</tr>
<tr>
<td></td>
<td>TOTAL</td>
<td>TOTAL</td>
</tr>
</tbody>
</table>
### Table 3. Randomizations Over Time

<table>
<thead>
<tr>
<th>Enrollment Month</th>
<th>Hospital 1</th>
<th>Hospital 2</th>
<th>Hospital 3</th>
<th>.................</th>
<th>Hospital H</th>
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<tr>
<td>2</td>
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<td>12</td>
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<td>TOTAL</td>
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### Table 4. Number Excluded by Entry Criterion

<table>
<thead>
<tr>
<th>Criterion</th>
<th>Hospital 1</th>
<th>Hospital 2</th>
<th>Hospital 3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>.................</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hospital 1</td>
<td></td>
<td></td>
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<td>Hospital 2</td>
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</tr>
</tbody>
</table>
Table 5. Baseline Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Hospital: 1  2 .........................H (N and %, or mean and standard deviation [SD])</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean Age</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asian</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Black</td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td></td>
<td></td>
</tr>
<tr>
<td>etc.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean Years of Education</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Etc.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 6. Blood Sample Results

<table>
<thead>
<tr>
<th>Test</th>
<th>Hospital: 1  2 .........................H N %   N %   N %</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abnormal CBC</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Out-of-range INR</td>
<td></td>
<td></td>
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</tbody>
</table>

Table 7. INR Values

<table>
<thead>
<tr>
<th>Test Location</th>
<th>Hospital: 1  2 .......... H (mean SD)</th>
<th>OVERALL Mean SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Home</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clinic by patient</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clinic by study staff</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clinic by AC clinic</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Table 8. Adverse Events

<table>
<thead>
<tr>
<th>Adverse Event Type</th>
<th>Hospital: 1 2 .......... H</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N %  N %  ...  N %</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>...</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 9. Medical History

<table>
<thead>
<tr>
<th>Condition</th>
<th>Hospital: 1 2 .......... H</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N %  N %  ...  N %</td>
<td></td>
</tr>
<tr>
<td>Bleeding disorder</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiac</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Etc.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 10. Termination from Study

<table>
<thead>
<tr>
<th>Reason for Termination</th>
<th>Hospital: 1 2 .......... H</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N %  N %  ...  N %</td>
<td></td>
</tr>
<tr>
<td>patient withdrew -- related to treatment assignment</td>
<td></td>
<td></td>
</tr>
<tr>
<td>patient withdrew -- unrelated to treatment assignment</td>
<td></td>
<td></td>
</tr>
<tr>
<td>patient moved away</td>
<td></td>
<td></td>
</tr>
<tr>
<td>patient lost to follow-up</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patient died</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td></td>
<td></td>
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<tr>
<td>Total</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Table 11. Number of Forms Received/Missing

<table>
<thead>
<tr>
<th>Form</th>
<th>Hospital: 1 2 .......... H</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N %  N %  ...  N %</td>
<td></td>
</tr>
<tr>
<td>01</td>
<td></td>
<td></td>
</tr>
<tr>
<td>02</td>
<td></td>
<td></td>
</tr>
<tr>
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<td></td>
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</tr>
<tr>
<td>...</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 12. Number of Forms Received with Errors

<table>
<thead>
<tr>
<th>Forms</th>
<th>Hospital: 1 2 .......... H</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number submitted</td>
<td>N %  N %  ...  N %</td>
<td></td>
</tr>
<tr>
<td>Number with missing data</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number with data out of range</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number randomized by mistake</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of invalid codes</td>
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</table>

Table 13. Patients with Study Outcomes

<table>
<thead>
<tr>
<th>Type</th>
<th>Hospital: 1 2 .......... H</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>PRIMARY</td>
<td>N %  N %  ...  N %</td>
<td></td>
</tr>
<tr>
<td>- Stroke TE</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Major bleed</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Death</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SECONDARY</td>
<td>N %  N %  ...  N %</td>
<td></td>
</tr>
<tr>
<td>- non-stroke TE</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- MI</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Minor bleed</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### Table 14. Time to First Event

<table>
<thead>
<tr>
<th>Type</th>
<th>Hospital: 1 2 .......... H</th>
<th>Mean (SD)</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>PRIMARY</td>
<td></td>
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<tr>
<td>- Stroke TE</td>
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<tr>
<td>- Major bleed</td>
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<td></td>
</tr>
<tr>
<td>- Death</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Overall</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SECONDARY</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- non-stroke TE</td>
<td></td>
<td></td>
<td></td>
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<td>- MI</td>
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<tr>
<td>- Minor bleed</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Overall</td>
<td></td>
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<td></td>
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</tbody>
</table>

### Table 15. Number of Unscheduled Visits

<table>
<thead>
<tr>
<th>Hospital: 1 2 .......... H</th>
<th>Mean</th>
<th>SD</th>
</tr>
</thead>
</table>

### Table 16. Satisfaction with Care

<table>
<thead>
<tr>
<th>Hospital: 1 2 .......... H</th>
<th>Mean</th>
<th>SD</th>
</tr>
</thead>
</table>

### Table 17. Quality of Life

<table>
<thead>
<tr>
<th>Hospital: 1 2 .......... H</th>
<th>Mean</th>
<th>SD</th>
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</thead>
</table>
Table 18. Health Care Utilization and Cost

<table>
<thead>
<tr>
<th>Hospital:</th>
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<th>2</th>
<th>.......</th>
<th>H</th>
<th>Mean (SD)</th>
<th>.....</th>
<th>Mean (SD)</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
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</tr>
<tr>
<td>- outpatient tests</td>
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</tr>
<tr>
<td>b. NON-VA</td>
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<td></td>
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<tr>
<td>- hospital admissions</td>
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<tr>
<td>a. PROVIDED BY VA</td>
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<td></td>
</tr>
<tr>
<td>b. NON-VA</td>
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<tr>
<td>- hospital admissions</td>
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<td></td>
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<tr>
<td>- outpatient tests</td>
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</tr>
</tbody>
</table>
XIV. DEVICE HANDLING PROCEDURE

Study meters and related materials will be shipped to the pharmacy at each study site, which will be responsible for the control and distribution of the meters and materials. The specific meter to be used in THINRS has FDA approval for the intended use and therefore THINRS will not be conducted under an IDE. But, the meters and materials must still be controlled and distributed in accordance with M-2 (Clinical Affairs) Part IV (Pharmacy Service), Chapter 6 Investigational Drugs.

Brief Study Design: All subjects will be provided with a meter during Part One. Individuals who demonstrate an ability to use the meter during Part One will be given the opportunity to participate in Part Two of THINRS. In Part Two, subjects will be randomized to test their INR with a meter at home or to continue to receive INR testing in a clinic. Subjects who were unable to use the meter in Part One, or who are randomized to the clinic-testing arm of the study for Part Two, will be returning meters for reuse by other subjects. Cleaning of the meter will be the responsibility of the site study coordinator, not the pharmacy.

The following materials will be provided for the THINRS study:

- The ProTime Microcoagulation System meter will be packaged in individual boxes with dimensions of approximately 16 x 8 x 5 ½ inches (LxDxH). Secondary to the design of the study, an individual meter may returned by one study subject and reassigned to another subject. Therefore each meter will be uniquely numbered and will require individual tracking accountability by meter. Documentation for this tracking will be provided by the CRPCC.

- ProTime Microcoagulation System ProTime3 cuvettes and Tenderlett Plus LV Meters: The cuvettes require refrigeration. Cuvettes and Tenderletts will come packaged in boxes of 25 cuvettes and 27 Tenderletts. Box dimensions are approximately 7 x 6 x 6 inches. The cuvettes and Tenderletts will require tracking for inventory purposes and for expiration dating. Documentation for this
tracking will be provided by the CRPCC. During Part One, study subjects will need less than an entire box of cuvettes/Tenderletts; therefore the study site will be responsible for repackaging and labeling of cuvettes and Tenderletts during Part One. The pharmacy will be given several options for control of the repacking to allow maximal flexibility within M-2, Part IV regulations and specific facility needs.

- A single meter carrying case will be provided for EACH meter (dimension of case package, 9 ¾ x 6 ½ x 3 ½ inches). There are NO provisions by THINRS to replace carrying cases that are not returned by a subject when a meters is returned, therefore the carrying case should be tracked with the meter. Documentation for this tracking will be provided by the CRPCC, but the cases will not be individually numbered.

While each study site will be provided with an initial stock of meters, carrying cases and cuvettes/Tenderletts, each study site will be responsible for providing inventory and reorder information to the CRPCC. Details of the inventory process are in development.
XV. POTENTIAL PARTICIPATING SITES

In 2002, a packet of materials containing information about CSP #481 was sent to the Director, Anticoagulation Clinic through the ACOS, Research and Development and the Chief, Cardiology Service at each VAMC to solicit their interest in participating in the study and to gather data on the estimated number of patients on warfarin and those who met the study entry criteria. The following table summarizes the results of this survey.

<table>
<thead>
<tr>
<th>VA</th>
<th>On Warfarin</th>
<th>Meet Eligibility Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Albany NY</td>
<td>1639</td>
<td>1311</td>
</tr>
<tr>
<td>Baltimore</td>
<td>800</td>
<td>320</td>
</tr>
<tr>
<td>Birmingham</td>
<td>600</td>
<td>300</td>
</tr>
<tr>
<td>Bronx</td>
<td>498</td>
<td>199</td>
</tr>
<tr>
<td>Buffalo</td>
<td>535</td>
<td>482</td>
</tr>
<tr>
<td>Cleveland</td>
<td>1400</td>
<td>910</td>
</tr>
<tr>
<td>Denver</td>
<td>621</td>
<td>311</td>
</tr>
<tr>
<td>Durham</td>
<td>411</td>
<td>259</td>
</tr>
<tr>
<td>Hines</td>
<td>1000</td>
<td>650</td>
</tr>
<tr>
<td>Iowa City</td>
<td>683</td>
<td>444</td>
</tr>
<tr>
<td>Kansas City</td>
<td>1000</td>
<td>450</td>
</tr>
<tr>
<td>Loma Linda</td>
<td>950</td>
<td>314</td>
</tr>
<tr>
<td>Madison</td>
<td>1000</td>
<td>400</td>
</tr>
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<td>Miami</td>
<td>300</td>
<td>150</td>
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<tr>
<td>Minneapolis</td>
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<td>North Chicago</td>
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<tr>
<td>Palo Alto</td>
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<td>420</td>
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<td>Providence</td>
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<td>500</td>
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<td>Reno</td>
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<td>287</td>
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<tr>
<td>Richmond</td>
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<td>510</td>
</tr>
<tr>
<td>Salem VA</td>
<td>532</td>
<td>532</td>
</tr>
<tr>
<td>Salt Lake City</td>
<td>970</td>
<td>582</td>
</tr>
<tr>
<td>San Antonio</td>
<td>400</td>
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<td>San Diego</td>
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<td>San Juan</td>
<td>473</td>
<td>284</td>
</tr>
<tr>
<td>Washington</td>
<td>500</td>
<td>250</td>
</tr>
<tr>
<td>West Haven</td>
<td>1779</td>
<td>890</td>
</tr>
<tr>
<td>West LA</td>
<td>750</td>
<td>450</td>
</tr>
</tbody>
</table>

Average 805 468
XVI. METHODS OF DETERMINING UTILIZATION AND COST

Because they require different methods, health care utilization and costs will be divided into three categories:

VA Health Care Costs: Health care provided within VA or provided outside VA but funded by VA.

Non-VA Health Care Costs: Health care outside VA that is not paid for by VA.

Other costs: Non health care costs such as patient travel time and lost wages.

Utilization and costs will be reported for the entire two years of follow-up and for subsets of this period.

A. Sources of Utilization Data

Table 8 presents a summary of the types of care included in each of the categories of health care, the measure of utilization and cost, and the sources of utilization and cost data. These data will be obtained for a period of two years following a patient's entry into the study. The following six sources of health care utilization data will be used:

Austin Automation Center (AAC). The main data sources for each study patient's use of VA services will be the centralized VA data maintained at the AAC. The AAC maintains SAS data sets that capture all VA inpatient (PTF) and outpatient (OPC) utilization. There are also data sets that track the use of non-VA care paid for by the VA (FEN). The PTF data have DRGs and the underlying ICD codes that will be the basis of the costs estimates.

Starting in FY 1997, the VA started coding at least one CPT-4 code per outpatient encounter. Thus, the OPC now contains sufficient information to make reasonable cost assignments. Staff at the Palo Alto CSPCC have conducted preliminary studies of the accuracy of these data. While they are not perfect, to date we have found the data quality to be quite high.

Patient Calendar. Patients will be asked to keep a calendar of all health care services (ambulatory, hospital, nursing home, home, and day care) received from non-VA sources. For hospitalizations (including long term care), we will ask the patient for the name of the facility, and have the patient sign a form authorizing the hospital to release data. We will use the patient reported information as the starting point for more detailed data abstraction. For non-VA outpatient care, the patient calendar will be the
extent of the data collection. Patients will be asked to classify outpatient encounters into simple categories of the type of outpatient encounter. The main purpose of these categories is to distinguish between less and more expensive outpatient visits. The categories will be: Primary care, Specialist medical care, Simple testing or lab work, Complex testing, Outpatient procedures, Other outpatient care. A sheet that includes examples of these categories will be included in the calendar that the study will provide to each patient for collecting these data. Patients will be reminded at each face-to-face visit to bring their calendar to the next face-to-face visit. Patients will also be mailed reminders prior to each VA face-to-face visit and the final interview at 24 months. Pertinent information from the calendar will be obtained by the research assistant during these contacts.
Table 8. Summary of Methods for Assessing Utilization and Cost of Care

<table>
<thead>
<tr>
<th>Service</th>
<th>Measure of Utilization</th>
<th>Cost</th>
<th>Source of Information on Utilization</th>
<th>Source of Information on Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>VA COSTS</strong></td>
<td></td>
<td></td>
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<tr>
<td>Health Care Within the VA</td>
<td></td>
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<tr>
<td>Ambulatory Clinic visits</td>
<td>Cost per visit</td>
<td>OPC</td>
<td>HERC</td>
<td></td>
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<tr>
<td>Laboratory Number of tests</td>
<td>Cost per test</td>
<td>DSS</td>
<td>DSS</td>
<td></td>
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<tr>
<td>Tests</td>
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<tr>
<td>Outpatient Number of tests</td>
<td>Cost per prescription</td>
<td>DSS</td>
<td>DSS</td>
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<tr>
<td>Pharmacy</td>
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<tr>
<td>Hospital: Admissions Length of stay</td>
<td>LOS adjusted</td>
<td>PTF</td>
<td>HERC</td>
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<tr>
<td>Medical-Surgical Admissions</td>
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<tr>
<td>Hospital: Other Inpatient Admissions</td>
<td>Cost per day</td>
<td>PTF</td>
<td>HERC</td>
<td></td>
</tr>
<tr>
<td>Home Care Number of visits</td>
<td>Cost per visit</td>
<td>Home care records</td>
<td>Medicare</td>
<td></td>
</tr>
<tr>
<td>Nursing Home Admissions Length of stay</td>
<td>Cost per day</td>
<td>Nursing home admission discharge form and PTF</td>
<td>HERC</td>
<td></td>
</tr>
<tr>
<td>Travel Miles</td>
<td>Cost per mile</td>
<td>PTF/OPC</td>
<td>IRS</td>
<td></td>
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<tr>
<td><strong>Health Care Outside VA and Paid by VA</strong></td>
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<td></td>
<td></td>
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<tr>
<td>Ambulatory Clinic visits</td>
<td>Cost per visit</td>
<td>AAC</td>
<td>HERC</td>
<td></td>
</tr>
<tr>
<td>Hospital Admissions Length of stay</td>
<td>LOS adjusted</td>
<td>AAC</td>
<td>HERC</td>
<td></td>
</tr>
<tr>
<td>Nursing Home Admissions Length of stay</td>
<td>Cost per day</td>
<td>AAC</td>
<td>Estimated VA per diem costs</td>
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<tr>
<td><strong>NON-VA COSTS</strong></td>
<td></td>
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<tr>
<td>Health Care Outside VA and Not Paid by VA</td>
<td></td>
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<td></td>
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</tr>
<tr>
<td>Ambulatory Office visits</td>
<td>Cost per visit</td>
<td>Patient calendar average</td>
<td>Study VA</td>
<td></td>
</tr>
<tr>
<td>Hospital Admissions Length of stay</td>
<td>Costs per admission</td>
<td>Patient calendar &amp; chart review</td>
<td>Medicare</td>
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<tr>
<td>Home Care Number of visits</td>
<td>Cost per visit</td>
<td>Patient calendar average</td>
<td>Study VA</td>
<td></td>
</tr>
<tr>
<td>Nursing Home Admissions Length of stay</td>
<td>Cost per day</td>
<td>Patient calendar average</td>
<td>Study VA</td>
<td></td>
</tr>
</tbody>
</table>
PATIENT COSTS

Travel Miles Cost per mile Patient encounter IRS
Lost Wages Hours Missed Hourly wage Patient report Patient report

DHCP: Decentralized Hospital Computer Program
DRG: Diagnosis-Related Groups
LOS: Length of Stay
PTF: Patient Treatment File
OPC: Outpatient Care File
AAC: Other data (besides PTF) at VA Austin Automation Center
DSS: Decision Support System

**VA Medical Center Records.** Because it is possible that some data will not be available from other sources (e.g. missing data), VA medical records will function as a back up data source. When information are not available from other sources, but we know that VA services were provided, the medical records of specific study patients will be examined to determine utilization. These data will be obtained by the site research assistant and transmitted to the CSPCC using the appropriate study forms. While this should not be required very often, previous studies have found the need to obtain data from patient charts on occasion.

**VA Outpatient Laboratory Utilization:** Because the intervention may effect laboratory use, this study will collect detailed information on the utilization of VA laboratories. These data are not included in the ACC data bases. While the VA is now coding CPT codes for outpatient encounters, a preliminary check using data from CSP 20 found that many laboratory tests were not being reported to Austin. Thus, we will collect these data using the Decision Support System (DSS) laboratory abstract.

**VA Outpatient Imaging Utilization:** The need for radiology procedures mirrors that of the laboratory data. Similarly, the quality of the CPT code data in the OPC has not been validated, but preliminary data checks have found much higher data quality than for laboratory tests. Unlike the VISTA laboratory data, the VISTA radiology module has been coding CPT codes for many years so CPT codes are available for these data.

**VA Outpatient Pharmacy Utilization:** The DSS has recently made available an outpatient pharmacy extract that provides encounter level data on the use of outpatient pharmacy use by each patient.
B. Sources of Cost Data

The primary source of data to estimate the costs of care will be HERC and DSS. HERC’s cost estimates are derived from Medicare reimbursement rates, scaled to actual VA costs (Wagner et al., 2001; Phibbs, et al., 2001). The HERC average cost data sets are updated each year after the ACC produces the final version of the Austin data sets; usually about 1 month after the end of the fiscal year. DSS cost estimates are drawn from an integrated accounting system. DSS extracts exist for pharmacy and laboratory encounters, areas where the data are incomplete in the Austin data bases. As noted above, DSS estimates will be scaled back to national averages so that they are comparable with the nationally based HERC cost estimates.

VA Pharmacy Costs: The costs of outpatient pharmacy services will be obtained from the DSS pharmacy extract. These cost estimates include the costs of the medication, the cost to fill each prescription, and overhead costs.

Contract, Payment Information Card, Fee Pharmacy Card. For health care outside the VA that is purchased by the VA, including pharmaceutical, the “Fee Base Files” at the AAC will be used to determine the amount paid by VA.

Patient Travel Costs and Lost Wages. At enrollment, each patient will be asked about their usual mode of transportation to receive VA care and how long it takes them to reach the VA facility. This information will be used to calculate patient travel costs to the study facility. If the patient uses care at another VA facility during the study, distance from the population centroid of patient’s zip of residence to the location of the VA facility will be used to calculate travel costs. For all non-VA utilization, the patient will be asked to report travel time and mode of transportation in the calendar. At enrollment the patient will also be asked if the patient must miss work for medical appointments. If the patient must miss work, the patient will be asked his/her wage rate to allow estimation of lost wages. If the patient reports that someone else accompanies them when they seek medical care, the questions about missing work and lost wages will be asked about the person who usually accompanies them on medical visits. These questions will also be asked at close out. If there are any changes from baseline, they will be asked when the changes occurred.
Patient Training Costs. The costs associated with training patients to use the test devices will be determined by the length of time it takes to run the training classes and the wage rates paid to the trainers. This will include the time spent preparing for the training sessions.

Phone Support Costs. The costs of the phone support for the intervention will be directly tracked from the study budget. The study will be setting up a phone support system, and thus, can directly track the costs of providing this service.

C. Calculation of Variables for Utilization and Cost

Table 8 summarizes the measures of cost and sources of cost information by type of health care. Most of the cost estimates will be obtained directly from HERC or DSS data.

Non-VA Service Costs Paid by the VA. The cost of these services (e.g. contract nursing home) will be the patient specific contract cost for the care provided. An appropriate cost for administering these programs will be added to the contract cost. We will also attempt to obtain sufficient data to use the same methods as for VA provided care. When this is not possible, average estimated costs for similar VA care will also be used as a sensitivity test.

Non-VA Service Costs Not Paid by the VA. For inpatient at non-VA hospitals, we will be obtaining sufficient data from the hospitals to allow the application of the same method as we will use for VA acute care. For outpatient services, the cost of services received outside the VA will be estimated as the average costs for study patients for comparable services from the VA, where the estimates of costs of VA services will be determined as described above. These average costs will be calculated for each of the types of outpatient services collected by the patient calendars. These costs will then be applied to the utilization reported on the patient calendars. If data from the proposed linkage of VA and Medicare data become available to this study, we will also use Medicare data as an additional source for utilization and costs of non-VA health services.
XVII. TRAINING OF STUDY PERSONNEL

A. Training of Study Personnel at the Study Kickoff Meeting

Site personnel (Site Investigators or SI’s and Study Coordinators or SC’s) will be trained by Dr. Jacobson and representatives of the meter companies at the kickoff meeting just prior to the start of the study.

1. SI’s need relatively minimal training in the actual use of the meter (30 to 60 minutes). The primary deficiency for most investigators will be the comprehension of the nuances of PT testing from a laboratory perspective. Areas that will need to be covered include:

   - Differences between whole blood and plasma testing
   - Performance & limitations of fingerstick testing
   - Perspective on tissue thromboplastin interference
   - Performance of quality control
   - Type of quality control and procedures for each:
     - On-board
     - External liquid
     - External electronic
   - INR comparisons between testing

2. SC’s will require the most extensive training which will essentially be “teach the instructor” training because they will have to be competent not only in understanding the protocol and meters but also how to train the ACS manager and the patients. Areas that will need to be covered include:

   - Basic principles of anticoagulation
   - Reason for therapy, and prescribed therapeutic range in INR units
   - Care and cleaning of monitor
   - Storage and handling of cuvettes
   - Verification of cuvette integrity
   - Use and dosing of monitor
   - Troubleshooting of monitor
   - Performance of quality control
   - Preparation and performance of fingerstick
   - Handling of error messages
Criteria for repeat testing
Recording results in diary
Reporting results to automated answering service

Some of these issues are generic and pertain to all monitors while others are meter dependent. Meter training can probably be handled in 4-6 hours, 1-2 hours of which would be in a combined session with all coordinators, then 3-4 hour in meter dependent break out sessions. Two presenters will be leading each break out session, one from the study staff and one from the company that makes the specific meter.

B. Training of Subjects in PST and Use of Meters

Patients will receive initial training during Part 1 of the study and additional refresher training as needed during Part 2. At least two individuals (the SC and AC managers) will be capable of providing PT training. Typically, sessions will consist of the SC and AC manager and up to six patients per session. Training will be coordinated with the Anticoagulation Management Service.

C. Post Kick-Off Meeting Training and Monitoring

Training will include

1. Regular monthly calls - every one or two months among the study staff (SI’s and SC’s) to review patient accrual and discuss any problems that may arise and suggested solutions.

2. Ad hoc assistants with specific site training issues, coordinated with the training office

3. Refresher training during the annual meeting

In addition to monitoring that occurs during regular conference calls, CSP will maintain a real-time log of INR values reported to the centralized automated reporting system. In
this way, we can monitor site compliance. A central server with Internet access would allow for centralized oversight of all sites to ensure that the sites were actually keeping up with the patients and contacting the patients if results were not being reported.

Staff support for each meter. While this can be coordinated with the manufacturer, it would not be prudent to rely entirely on industry or there will be much greater potential for differences between sites in the amount of support they receive.
APPENDICES

A. MAST ACS Assessment Checklist

B. MAST Operations Manual
### A. MAST ACS Assessment Checklist

<table>
<thead>
<tr>
<th>Overall Criteria</th>
<th>Assessment Indicators</th>
<th>Met? (Yes/No)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>A. Structure</strong></td>
<td>1. Are there standardized forms for intake visit? (Flow sheets/referral forms, etc.)</td>
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<td></td>
<td>2. Do ACS personnel hold licenses in patient-oriented health care fields? (i.e., NP, RN, PA, PharmD)</td>
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<td></td>
<td>3. Have ACS personnel shown minimum competencies? (Traineeship? Standard curriculum? Examination/demonstration?)</td>
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<td></td>
<td>4. Have written guidelines for ACS management been established and approved by referring physicians?</td>
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<td>5. Are INR’s used?</td>
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<td></td>
<td>6. Does the ACS annual program evaluation include the contribution of various processes to patient outcomes? (i.e., INR levels? Bleeding rates? Thromboembolism rates?)</td>
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<tr>
<td><strong>B. Process of Care</strong></td>
<td>1. Is the INR measured within 7 days of initiation of anticoagulant therapy?</td>
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<td></td>
<td>2. Is the target range documented? (i.e., 2.0 to 3.0)</td>
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<td></td>
<td>3. Is the duration of therapy documented?</td>
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<td></td>
<td>4. Are patients whose INR’s are within target range scheduled for follow-up at 4 weeks or less?</td>
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<td>5. Is the response to moderately/extremely out of range INR’s correct? (Action, communication with patient, communication with MD, documentation)</td>
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<td></td>
<td>6. What percentage of visits have appropriate communication with patients?</td>
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<td></td>
<td>7. Are all health related problems triaged back to referring physician within 24 hours?</td>
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<td></td>
<td>8. Is each interaction with the patient documented?</td>
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<td></td>
<td>9. Is the proper procedure followed for no-shows?</td>
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<td></td>
<td>10. Is a reason given when ACS management is ended?</td>
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</tbody>
</table>
11. Is this reason provided to the referring physician?

12. Is the reason documented?

13. Was an educational plan prepared at the intake visit?
14. Is patient understanding of the educational plan documented?

C. Outcomes: Patients

1. What percentage of the time are INR’s -
   a. within target range?
   b. moderately out of range?
   c. extremely out of range?

2. What is the rate of thromboembolism?

4. What is the satisfaction level of the patients? (survey)

D. Outcomes: Payor

1. How many patients are anticoagulated?

2. Is the ACS cost-effective?