June 18, 2007

VIA Electronic Mail submission to: steve.phurrough@cms.hhs.gov

Stephen Phurrough, M.D., M.P.A.
Director, Coverage and Analysis Group
Center for Medicare and Medicaid Services
C1-13-18
7500 Security Boulevard
Baltimore, Maryland 21244-1850

Re: Formal request for reconsideration for home prothrombin time INR monitoring for anticoagulation management (NCD 190.11)

Dear Dr. Phurrough:

On behalf of the Prothrombin-Time Self Testing (PST) Coalition, we are writing to request a formal reconsideration of the above-captioned National Coverage Determination for home prothrombin time/International Normalized Ratio (PT/INR) monitoring. The PST Coalition comprises Hemosense Corporation, International Technidyne Corporation and Roche Diagnostics Corporation, the developers and manufacturers of home prothrombin time (PT/INR) devices cleared for marketing by the U.S. Food and Drug Administration. The PST Coalition members worked closely with CMS from 1997 through 2002 on the development and implementation of the current coverage policy for home PT/INR monitoring.

We are requesting a reconsideration of NCD 190.11 to expand the population eligible for coverage to patients on warfarin home PT/INR monitoring without regard for the underlying condition that determines the need for warfarin, as the black box warning on the label for warfarin states that "*Regular monitoring of INR should be performed on all treated patients.*" In the alternative, we would seek expansion of coverage to patients on warfarin home PT/INR monitoring whose underlying condition determining the need for warfarin includes atrial fibrillation or deep vein thrombosis (i.e., beyond current coverage among those with mechanical heart valves). Our request to expand coverage would leave in tact the requirements that the patient has been anticoagulated for at least three months, must undergo an educational program on anticoagulation management and the use of the device, and self-testing is limited to no more frequently than once a week.

Substantial new clinical evidence supporting the use of home PT/INR monitoring has been published since the Medicare Decision Memorandum was published in September 2001. In the attached coverage reconsideration request, we present 16 papers reporting results of 15 clinical studies published since 2000 that evaluate the effectiveness and safety of home PT/INR monitoring and include patients with underlying indications for warfarin beyond mechanical heart valves alone. This evidence base supports a conclusion that home PT/INR monitoring is at least as effective and safe as in-clinic monitoring in maintaining PT/INR levels within target range and reducing the incidence of major hemorrhagic and thromboembolic complications. Studies limited to patients with atrial fibrillation as well as those enrolling elderly patients support a determination that home PT/INR monitoring is effective and safe in these populations. In addition, analysis of studies by indication did not show that underlying reason for warfarin is associated with outcomes. Moreover, a broad range of additional studies included patients with conditions other than mechanical heart valves, including atrial fibrillation and deep vein thrombosis. In addition, studies limited to the elderly as well as analysis of other studies by age did not show age as a predictor of outcome.

Attached to this cover letter is all the information required to support this NCD reconsideration request consistent with the requirements described in the Federal Register Notice: Revised Process for Making Medicare National Coverage Determinations (68 Fed Reg. 55634, 55636-55637 [September 26, 2003][3062-N]).

Please contact our reimbursement counsel, Paul Radensky, M.D., J.D., at 305.347.6557 (or by e-mail at pradensky@mwe.com), if you have any questions regarding this reconsideration request. We look forward to working with you and your staff on this request.

Sincerely yours,

/s/ Larry Cohen

Larry Cohen
President
International Technidyne Corporation

/s/ David Phillips

David Phillips
Vice President, Marketing
HemoSense, Inc.

/s/ John Ridge

John Ridge
Director, Reimbursement Affairs
Roche Diagnostics Corporation

Attachments
Cc: Denise Garris, American College of Cardiology
Paul Radensky, M.D., J.D., McDermott, Will & Emery LLP

RECONSIDERATION REQUEST: NCD 190.11—HOME PROTHROMBIN TIME INR MONITORING FOR ANTICOAGULATION MANAGEMENT

I. A full and complete description of the item or service in question.

Home prothrombin time/International Normalized Ratio (PT/INR) monitoring comprises self-testing by patients or their caregivers of the INR, a measure that allows physicians to determine the level of anticoagulation in a patient treated with warfarin sodium. Use of the INR is intended to provide physicians with a standardized measure of anticoagulation independent of the specific reagents used by a particular laboratory. Maintaining patients within a therapeutic INR range minimizes the risk of adverse events associated with inadequate or excessive anticoagulation, such as thromboembolic events (e.g., recurrent deep vein thrombosis, pulmonary embolism, stroke) or serious bleeding.

The Medicare program commenced coverage of home PT/INR monitoring in 2002 based upon a determination that "Patient self-testing and self-management through the use of a home INR monitor may be used to improve the time in therapeutic ra[nge] (TTR) for select groups of patients. Increased TTR leads to improved clinical outcomes and reductions in thromboembolic and hemorrhagic events." (See Decision Memorandum—Tab C-1)

Home anticoagulation monitoring is covered as a diagnostic service (Social Security Act § 1861(s)(3)), and is paid under the Medicare Physician Fee Schedule (when provided from a physician office or independent diagnostic testing facility) and the Hospital Outpatient Prospective Payment System (OPPS)(when provided from a hospital outpatient clinic). Home PT/INR monitoring involves the furnishing, by a physician, IDTF or hospital clinic, of a PT/INR monitor (a prothrombin time test meter), test strips to run in the monitor, lancets for collecting blood samples, and alcohol swabs for preparing the skin for the self-testing of prothrombin time by patients or their caregivers at home (or otherwise outside the physician's office setting) on a weekly basis[1]. Home PT/INR monitoring is reported under the following three HCPCS codes to include the technical component service described above as well as an initial training session and physician review and interpretation of the test results:—

Code	Descriptor
G0248	Demonstration, at initial use, of home INR monitoring for patient with mechanical heart valve(s) who meets Medicare coverage criteria, under the direction of a physician; includes: demonstrating use and care of the INR monitor, obtaining at least one blood sample, provision of instructions for reporting home INR test results, and documentation of patient ability to perform testing
G0249	Provision of test materials and equipment for home INR monitoring to patient with mechanical heart valve(s) who meets Medicare coverage criteria; includes provision of materials for use in the home and reporting of test results to physician; per 4 tests

[1] The coverage policy limits coverage to testing no more than once per-week. The 4-test payment units under codes G0249 and G0250 may reflect weekly testing over a 4 week period or less frequent testing over a longer period. Medicare instructions to hospitals permit hospitals to report code G0249 as 3 units—i.e., 12 weekly tests. CMS allows hospitals to report this way because patients must be physically present at the hospital at the time these services are billed and it was assumed that patients would otherwise attend the hospital approximately every 3 months for evaluation and management of their anticoagulation and/or underlying condition.

Code	Descriptor
G0250	Physician review, interpretation and patient management of home INR testing for a patient with mechanical heart valve(s) who meets other coverage criteria; per 4 tests (does not require face-to-face service)

II. A specific, detailed description of the proposed use of the item or service, including the target Medicare population and the medical condition(s) for which it can be used.

Patients require chronic anticoagulation therapy with warfarin sodium for the following indications: (1) prophylaxis and/or treatment of venous thrombosis and pulmonary embolism, (2) prophylaxis and/or treatment of the thromboembolic complications associated with atrial fibrillation, (3) prophylaxis and/or treatment of the thromboembolic complications associated with cardiac valve replacement; and (4) to reduce the risk of death, recurrent myocardial infarction, and thromboembolic events such as stroke or systemic embolization after myocardial infarction. (See package insert for Coumadin® [warfarin sodium]—Tab D) For many of these indications, chronic therapy with warfarin is required.

Warfarin has a very narrow therapeutic range. Dosing of warfarin is highly individualized, and may be affected by factors such as other drugs and dietary sources of vitamin K. Proper dosing with warfarin requires periodic determination of the PT/INR level. The package insert for warfarin notes that the elderly are particularly sensitive to the effects of warfarin:

> *"Patients 60 years or older appear to exhibit greater than expected PT/INR response to the anticoagulant effects of warfarin. The cause of the increased sensitivity to the anticoagulant effects of warfarin in this age group is unknown. This increased anticoagulant effect from warfarin may be due to a combination of pharmacokinetic and pharmacodynamic factors. Racemic warfarin clearance may be unchanged or reduced with increasing age. Limited information suggests there is no difference in the clearance of S-warfarin in the elderly versus young subjects. However, there may be a slight decrease in the clearance of R-warfarin in the elderly as compared to the young. Therefore, as patient age increases, a lower dose of warfarin is usually required to produce a therapeutic level of anticoagulation."*

The package insert for warfarin was recently revised to include the following "Black Box" warning—

WARNING: BLEEDING RISK

Warfarin sodium can cause major or fatal bleeding. Bleeding is more likely to occur during the starting period and with a higher dose (resulting in a higher INR). Risk factors for bleeding include high intensity of anticoagulation (INR >4.0), age ≥65, highly variable INRs, history of gastrointestinal bleeding, hypertension, cerebrovascular disease, serious heart disease, anemia, malignancy, trauma, renal insufficiency, concomitant drugs (see **PRECAUTIONS**), and long duration of warfarin therapy. Regular monitoring of INR should be performed on all treated patients. Those at high risk of bleeding may benefit from more frequent INR monitoring, careful dose adjustment to desired INR, and a shorter duration of therapy. Patients should be instructed about prevention measures to minimize risk of bleeding and to report immediately to physicians signs and symptoms of bleeding (see **PRECAUTIONS: Information for Patients**).

These statements combined make clear that elderly patients are particularly sensitive to the effects of warfarin and that dosing should be adjusted carefully in this population based upon regular or more

frequent INR monitoring. These recommendations are independent of the underlying condition for which warfarin is prescribed.

Home PT/INR monitoring is performed using devices that have been cleared by the FDA for quantitative PT testing in fresh capillary blood by suitably selected and properly trained patients (or their caregivers) on the prescription of a physician. The intended use of these devices in the self-testing of PT/INR levels is independent of the underlying condition for which warfarin is prescribed.

In this reconsideration request, we are seeking an expansion of coverage to include suitably selected and properly trained patients on chronic warfarin therapy without limitation as to the underlying condition for which warfarin therapy is prescribed. In the alternative, we are seeking an expansion of coverage to suitably selected and properly trained patients whose underlying condition determining the need for warfarin includes atrial fibrillation or deep vein thrombosis (i.e., beyond current coverage among those with mechanical heart valves).

III. A compilation of the supporting medical and scientific information currently available that measures the medical benefits of the item or service. This may include portions of primary study data that have been separately submitted to the FDA as part of its submission package and are deemed most relevant for our review.

A. Introduction

Medicare has covered home PT/INR monitoring for patients with mechanical heart valves since 2002 (Medicare National Coverage Decisions Manual, Chapter 1, Part 3, § 190.11). The basis for coverage was explained in a Decision Memorandum dated September 18, 2001, which included a review of 11 published studies of home INR monitoring comprising over 2,000 patients: 7 randomized controlled trials, 2 cohort studies and 2 case-control studies.[2] All of these trials included patients whose underlying indication for treatment with warfarin was the presence of a mechanical heart valve. Six trials also included patients with other indications for warfarin, including atrial fibrillation (4 trials) and other conditions (5 trials), but over 90-percent of the patients in the studies reviewed had mechanical heart valves. Based upon these data, the determination was made to cover home PT/INR monitoring in patients with mechanical heart valves.

Adoption and use of home PT/INR monitoring in the Medicare population has been very limited. The Part B Extract and Surveillance and Survey System (BESS) data for 2005 show only 910 claims for training of new patients to perform home PT/INR monitoring (code G0248). The codes for ongoing monitoring (G0249 for the technical component service and G0250 for the professional component service) suggest that no more than 2,000 Medicare patients are currently performing home PT/INR monitoring under the existing coverage determination; this is likely less than 1% of the eligible population.[3] We understand from discussions with anticoagulation clinics that the limited adoption and use of this service is due, in part, to the limited scope of coverage. Representatives from several clinics have indicated to us that they would be more likely to adopt home PT/INR monitoring if coverage were

[2] The text of the Decision Memorandum identifies 10 studies: 8 randomized controlled trials, one cohort study and one case control study (White (1989), Ansell (1995), Hasenkam (1995), Horstkotte (1996), Sawicki (1999), Beyth (2000), Cromheecke (2000), Watzke (2000), Koertke (2000)). Reference is made to "Appendix A," but we have not been able to locate this appendix.

[3] BESS 2005 reveals 12,926 claims for G0249 and 2,778 claims for G0250. If we assume that billing for code G0250 is lower than actual utilization given the relatively low payment for this service ($9.47 [2005]), and considering that the ongoing monitoring code G0249 reflects blocks of 4 tests (approximately 4 weeks of monitoring), we would estimate that approximately 1,000 patients would be monitoring if this reflects patients testing all through 2005 and 2,000 patients if it reflects (on average) patients who started monitoring midway through the year.

extended to a broader segment of their clinic population. The limited scope of the benefit means they would have to undertake substantial time and expense to set up systems for home monitoring and reporting for a very small pool of patients (the revenues would not be sufficient to support the expense). More importantly, when they evaluate patients for home monitoring, their assessment is based upon need for frequent monitoring and the ability and interest of patients (or their caregivers) to perform home monitoring. Their assessment is unrelated to the underlying condition for which warfarin is prescribed, and they would want to offer the service to suitable candidates without limiting it to patients with mechanical heart valves.

The need for PT/INR monitoring and the potential for benefit from home monitoring is based upon the state of chronic anticoagulation due to warfarin—not the underlying cardiovascular condition for which warfarin is prescribed. Patients who require chronic warfarin therapy for atrial fibrillation, deep vein thrombosis or other thrombophilic conditions also require regular monitoring of PT/INR level to avoid thromboembolic and hemorrhagic complications of warfarin therapy. This leads to the question as to whether there now are data to support use of home PT/INR monitoring among patients on warfarin for conditions other than mechanical heart valves and to support a request to reconsider the current NCD to seek an expansion to cover patients with indications for warfarin beyond mechanical heart valves. Therefore, we conducted a review of the clinical evidence on home PT/INR monitoring published since the release of the 2001 Decision Memorandum focusing specifically on evidence in patients on warfarin for reasons beyond mechanical heart valves and focusing on patients ages 65 and older.

B. Methods

We conducted a search of the peer-review clinical literature to identify studies investigating home PT/INR monitoring that were published since 2001 and reviewed these papers specifically to assess inclusion of patients with atrial fibrillation, deep vein thrombosis or other indications for warfarin and to assess outcomes in patients aged 65 and older.

We conducted a search of the PubMed database covering the period from 2001 through May 2, 2007 for English language clinical trials, randomized clinical trials or meta-analyses involving humans using the following search terms: (1) *"anticoag*"*[4] or *"warfarin"* or *"coumarin*"* with (2) *"INR"* or *"prothrombin"* or *"PT"* or *"international normal* ratio"* with (3) *"self"*.

This search strategy identified 33 published papers. From this database we excluded the following: 12 papers that did not report results from clinical trials involving home PT/INR monitoring6 papers that reported studies limited to patients with mechanical heart valves, 1 study that involved a comparison of a new home PT/INR monitoring system to an established home PT/INR system, and 1 study in pediatric patients with congenital heart disease. In addition, the results of one study were presented in two separate reports: the core clinical results were presented first (Gadisseur 2003) and quality of life outcome measures from the same study were reported subsequently (Gadisseur 2004). This resulted in 13 papers reporting 12 clinical trials and meta-analyses of home PT/INR monitoring and that included patients with atrial fibrillation, deep vein thrombosis, or other indications for warfarin beyond mechanical heart valves. From review of these 13 papers, we identified 2 additional reports of clinical studies involving elderly patients or patients with atrial fibrillation that were published in 2000 and were not reviewed in the 2001 Decision Memorandum. In addition, a recent report from a study of self-management of oral anticoagulation in the elderly was identified and was considered important to include in this evidence review. Therefore, we include a total of 16 published reports to support this reconsideration request. (See Tab B)

[4] The asterisk (*) is used as a wild-card character to identify any wordstem with the characters to the left of the asterisk.

An evidence table including the publication citation, study design, patient population, results and conclusions/limitations for each of the 15 papers identified by our research strategy as summarized above is presented in Tab A. In section III.C., below, we summarize the findings from a 2006 meta-analysis of 14 studies, reported in *The Lancet*, and then summarize the available evidence from the studies in patients with atrial fibrillation (11 studies—section III.D), deep vein thrombosis (8 studies—section III.E), and patients ages 65 and older (4 studies—section III.F).

C. Meta-analysis findings

Heneghan, *et al*. (2006) published their findings from conducting a meta-analysis of 14 randomized trials involving 3,049 participants who were performing self-monitoring of oral anticoagulation. Nine (9) trials involved 1,936 patients on long-term anticoagulation without limitation to any specific underlying indication for anticoagulation (White, *et al.* 1989, Sawicki, *et al.* 1999, Beyth, *et al.* 2000, Cromheecke, *et al.* 2000, Fitzmaurice, *et al.* 2002, Gadisseur, *et al.* 2003, Gardiner, *et al.* 2004, Sunderji, *et al.* 2004, and Menéndez-Jándula, *et al.* 2005); 2 trials (281 patients) were limited to patients on anticoagulation for atrial fibrillation (Khan, *et al.* 2004 and Voller, *et al.* 2005); and 3 trials (832 patients) were limited to patients on anticoagulation for mechanical valves (Horstkotte, *et al.* 1998, Kortke, *et al.* 2001, and Sidhu, *et al.* 2001). Nine (9) of these studies were not included among the studies reviewed in the September 18, 2001 Decision Memorandum; 5 studies were included in the 2001 review. The 9 new studies were published between 2000 and 2005.

Meta-analyses were performed with regard to thromboembolic outcomes, major hemorrhage outcomes, and death looking at the overall population and looking at subsets that self-monitored only or that self-monitored and self-adjusted their anticoagulant dosages. The findings are summarized in the table below:

Table 1
Meta-Analysis Outcomes with Self-Monitoring (Heneghan 2006)
Odds Ratios* (95% CI)

	Self-monitor	Self-monitor+ Self-adjust	Overall
Thromboembolic events	0.57 (0.35-0.93)	0.27 (0.12-0.59)	0.45 (0.30-0.68)
Hemorrhagic events	0.56 (0.34-0.93)	0.93 (0.42-2.05)	0.65 (0.42-0.99)
Death	0.81 (0.44-1.49)	0.37 (0.16-0.85)	0.61 (0.38-0.98)

*Odds ratios <1 favor self-monitoring (with/without self-adjusting); odds ratios >1 favor control

These analyses showed statistically significant reductions in favor of self-monitoring with or without self-adjustment (overall group) in the odds of thromboembolic events, hemorrhagic events and death. Pooling of the efficacy data with regard to INR results within target range was not possible because information was obtained in two different ways: either the proportion of overall tests in range or the proportion of tests of each individual in range.

Heneghan, *et al*. did not conduct any subset analyses investigating outcomes by underlying reason for warfarin, but they did report the outcomes for each study allowing us to show the numbers and outcomes for those studies that included patients with indications for warfarin beyond mechanical heart valves, as shown in the table below.

Table 2
Meta-analysis—Individual Study Results—Mixed Indications/Atrial Fibrillation

Study	N	Duration of study (months)	Mean Age (years)	% Within Range (Mean INR or Time)†† Self Control (p-values)	Thromboembolic Odds Ratio (95%CI)	Hemorrhagic Odds Ratio (95%CI)	Death Odds Ratio (95%CI)
White (1989)†	50	2	50	87% 68% (p<0.001)	0.30 (0.01-7.61)	Not estimable*	Not estimable*
Sawicki (1999)†	165	6	55	53% 43.2% (p=0.22)	0.19 (0.01-4.08)	0.99 (0.06-16.06)	0.99 (0.06-16.06)
Beyth (2000)	325	6	75	56% 32% (p<0.001)	0.63 (0.31-1.29)	0.44 (0.18-1.05)	0.77 (0.42-1.44)
Cromheecke (2000)†	98	3	42	55% 49% (p=0.06)	0.33 (0.01-8.22)	Not estimable*	Not reported
Fitzmaurice (2002)	49	6	63	74% 77% (p=NS)	Not estimable*	0.36 (0.01-9.32)	0.36 (0.01-9.32)
Gadisseur (2003)	320	6	57	65% 61.3% (p=0.14)	Not estimable*	0.70 (0.03-17.51)**	Not reported
Gardiner (2004)	53	6	58	61% 64% (p=NS)	Not estimable*	Not estimable*	2.58 (0.10-66.24)
Khan (2004)	79	6	73 (median)	71.1% 70.4% (p=NS)	Not reported	Not reported	Not reported
Sunderji (2004)	139	8	60	71.8% 63.2% (p=0.14)	0.20 (0.01-4.18)	0.33 (0.01-8.32)	Not estimable*
Menendez-Jandula (2005)	737	11.8***	66	64.3% 64.9% (p=0.2)	0.19 (0.06-0.57)	0.57 (0.16-1.96)	0.39 (0.15-1.02)
Voller (2005)	202	5	64	67.8% 58.5% (p=0.0061)	0.33 (0.01-8.20)	3.03 (0.12-75.26)	Not estimable*

† Study included in the 2001 Decision Memorandum
††Where % in range reported both for mean INR and time, time in therapeutic range is reported in this table
*Zero events in both self-monitoring and control groups; odds ratios not estimable.
** Odds ratio shown in table is for self-monitoring subgroups. Odds ratio (95% CI) for self-monitoring plus self-adjusting subgroups=2.40 (0.33-17.57).
*** Median duration of observation period as reported in publication

Percent INR in therapeutic range (mean INR or time in range) was either significantly greater in the self-monitoring group compared with control or there was no significant difference between groups. Although adverse outcome odds ratios were not significant in the individual trials, nearly all of the odds ratios favored self-monitoring with lower events than in the control groups. In addition, although follow up ranged from 2 to 11.8 months—a period of time over which few major adverse events would be expected—significant differences in events were observed favoring self-monitoring.

D. Atrial fibrillation

There were 14 studies that provided evidence supporting the use of home PT/INR monitoring in patients with atrial fibrillation. These included 2 randomized trials with enrollment limited to patients with atrial

fibrillation, 2 randomized trials that enrolled subjects with various indications for warfarin (mixed population) and analyzed outcomes by indication for anticoagulation and 1 retrospective study that included patients with atrial fibrillation or deep vein thrombosis. Nine additional randomized studies included a mixed population of subjects including patients with atrial fibrillation.

Studies Limited to Patients with Specific Underlying Conditions—Atrial Fibrillation

Völler, *et al*. (2005a), reported the results of a multi-center trial investigating whether the quality of anticoagulation treatment could be improved by self-management compared to conventional management by the physician. As designed, the trial was intended to randomize 2000 patients into the two arms of the study. However, during the 19 month enrollment period (December 1999 to July 2001) the investigators enrolled only 202 patients, and the study was discontinued prematurely due to limited enrollment. Despite the limited enrollment, the investigators did find a statistically significant difference between groups in the percent of INR values that were within target range: self-management 67.8% versus usual care 58.5% ($p=0.0061$). The self-management group showed significantly lower percent INR values below target range (15.2%) compared with usual care (22.1%)($p=0.0379$). Patients in the self-management group spent more time within target range (178.8 days) than the usual care group (155.9 days), but this difference was not statistically significant between groups.

Khan, *et al*. (2004), reported the results of a randomized trial of 125 patients with atrial fibrillation who were 65 years and older and had taken warfarin for at least 12 months. Patients were randomized to either routine clinic care, education and clinic care, or education and self-monitoring. Patients in the education and self-monitoring group showed a statistically significant improvement in percent-time in therapeutic range (mean difference 14.1%; 95% CI 6.7-21.5%; $p<0.001$). By contrast changes in the education and clinic monitoring and routine clinic monitoring groups did not show statistically significant improvements (education and clinic—mean difference 8.8%; 95% CI -0.2-17.8%; $p=0.054$; routine clinic—mean difference 3.2%; 95% CI -7.3-13.7%; $p>0.5$). The differences in percent-time in therapeutic range between groups were not statistically significant because of the large variability in this measure.

Studies Analyzing Data by Indication—Atrial Fibrillation

Menéndez-Jándula, *et al*. (2005), compared self-management of oral anticoagulation therapy with clinic management in 737 patients with various indications for anticoagulation. Approximately 50-percent of the study population included patients taking oral anticoagulants for atrial fibrillation, dilated cardiomyopathy, valve disease, or biological prosthesis; the remaining patients had mechanical heart valves (36-percent) or venous thrombosis (13.6-percent). The overall results from the study are reported in the evidence table (Tab A – Item 2.7). The investigators observed no relationship between the percentage of INR tests within target range and indication for oral anticoagulation therapy.

A second study by Voeller, *et al*. (2005b) reported the results of a 330 patient study comparing education and clinic management versus education and self-management of anticoagulation. This was a non-randomized study; patients were assigned to group based upon suitability or non-suitability for self-management of anticoagulation. Ninety-eight patients (29.7%) had atrial fibrillation. The overall results from this study are also reported in the evidence table (Tab A – Item 2.5). The investigators determined that indication for anticoagulation therapy was not significant with regard to complication rate between self-management and usual care.

Heidinger, *et al.* (2000) published their findings from a retrospective study 1,375 patients on long-term self-management of anticoagulation in the treatment of atrial fibrillation or deep vein thrombosis. The study included a cohort of 753 patients with atrial fibrillation. Among patients with atrial fibrillation, hemorrhagic complications were observed at a rate of 1.69-percent per patient-year while

thromboembolic complications were observed at a rate of 1.04-percent per patient-year. 69.47-percent of INR values were in therapeutic range among patients with atrial fibrillation. The authors observed: "The rate of complications found in this study is in accordance with or even better than the results of other groups who investigated mainly patients with heart valve replacement who perform self-management or self-testing."

Studies with Mixed Populations—Including Atrial Fibrillation

In addition to studies limited to patients with atrial fibrillation or that included specific analyses by indication, 9 of the studies identified in our search strategy included patients with atrial fibrillation. The results of these studies are included in the evidence table at Tab A and support the effectiveness and safety of home PT/INR monitoring. These studies and the number and percent of patients in the studies with atrial fibrillation are presented below.

Study Citation	N	Atrial Fibrillation n (%)
Siebenhofer, *et al.* (2007)	195	89 (46)
Fitzmaurice, *et al*. (2005)	617	NS*
Gardiner, *et al*. (2005a)	84	23 (27)
Gardiner, *et al*. (2005b)	104	42 (40)
Sunderji, *et al*. (2004)	139	40 (29)
Gadisseur, *et al*. (2003)	320	68 (21)
Fitzmaurice, *et al.* (2002)	49	27 (55)
Oral Anticoagulation Monitoring Study Group (2001)	82	14 (17)
Beyth, *et al*. 2000	325	54 (17)

*The number and proportion of patients with atrial fibrillation was not specified by the investigators in this study, however, atrial fibrillation was the most common diagnosis among patients in the trial.

E. Deep vein thrombosis

There were a total of 11 studies that provide evidence supporting the use of home PT/INR monitoring in patients with deep vein thrombosis. There were no studies limited to patients with deep vein thrombosis; 1 randomized trial enrolled subjects with various indications for warfarin and analyzed outcomes by indication for anticoagulation and 1 retrospective study that included patients with deep vein thrombosis or atrial fibrillation. Nine additional randomized studies included a mixed population of subjects including patients with deep vein thrombosis.

Studies Analyzing Data by Indication – Deep Vein Thrombosis

Menéndez-Jándula, *et al*. (2005)(see Section III.D.), compared self-management of oral anticoagulation therapy with clinic management in 737 patients with various indications for anticoagulation. Approximately 14-percent of the study population included patients taking oral anticoagulants for venous thrombosis. The overall results from the study are reported in the evidence table (Tab A – Item 2.7). The investigators observed no relationship between the percentage of INR tests within target range and indication for oral anticoagulation therapy.

Heidinger, *et al.* (2000)(see Section III.D.) published their findings from a retrospective study 1,375 patients on long-term self-management of anticoagulation in the treatment of deep vein thrombosis or atrial fibrillation. The study included a cohort of 622 patients with deep vein thrombosis. Among patients with deep vein thrombosis, hemorrhagic complications were observed at a rate of 1.52-percent per patient-year while thromboembolic complications were observed at a rate of 1.21-percent per patient-

year. 69.18-percent of INR values were in therapeutic range among patients with deep vein thrombosis. As noted above, the authors observed that the rate of complications found in their study in patients with deep vein thrombosis and atrial fibrillation were consistent with or better than results from previous studies that investigated mainly patients with mechanical heart valves.

Studies with Mixed Populations—Deep vein thrombosis

Eight studies identified in our search strategy reported inclusion of patients with deep vein thrombosis. The results of these studies are included in the evidence table at Tab A and support the effectiveness and safety of home PT/INR monitoring. These studies and the number and percent of patients in the studies with deep vein thrombosis are presented below.

Study Citation	N	Deep Vein Thrombosis n (%)
Siebenhofer, *et al.* (2007)	195	35 (37)
Fitzmaurice, *et al*. (2005)	617	NS*
Gardiner, *et al*. (2005)	104	20 (19)
Voeller, *et al*. (2005)	330	15 (5)
Gardiner, *et al*. (2004)	84	24 (29)
Sunderji, *et al*. (2004)	139	10 (7)
Gadisseur, *et al*. (2003)	320	65 (20)
Beyth, *et al*. (2000)	325	124 (38)
Oral Anticoagulation Monitoring Study Group (2001)	82	13 (16)

*The number and proportion of patients with deep vein thrombosis was not specified by the investigators in this study, however, deep vein thrombosis/pulmonary embolism was the third most common diagnosis among patients in the trial.

F. Elderly populations

There were 5 studies that provide evidence specifically supporting the use of home PT/INR monitoring in elderly patients (≥65 years of age). These included 3 randomized trials with enrollment limited to elderly patients and 2 additional studies that discussed results in relation to age. In addition, all of the other studies included in the evidence table (Tab A) included elderly patients among the study population.

Studies in the Elderly

Beyth, *et al*. 2000, conducted a randomized controlled trial in 325 patients 65 years of age or older (mean age 75 years; range 65 to 94 years) who started warfarin therapy during an inpatient hospitalization. Patients were stratified according to baseline risk for major bleeding and were randomly assigned to receive an intervention comprising education and self-monitoring or usual care. The intervention consisted of patient education about warfarin, training to increase patient participation, self monitoring of prothrombin time, and guideline-based management of warfarin dosing. The study follow-up period was 6 months. The patient population comprised those receiving warfarin for deep vein thrombosis (38%), atrial fibrillation (17%), cerebrovascular disease (15%), prosthetic heart valves (11%), peripheral vascular disease (4%), myocardial infarction (2%) and other thombophilia (13%).[5] Over the study period, the proportion of total treatment time during which the INR was within the therapeutic range was higher in

[5] Underlying conditions for warfarin included in the "other" category (total=41 patients) were other venous clots (12), congestive heart failure (8), other arterial clots (7), left ventricular clots (6), systemic emboli (4), and left ventricular aneurysm or aneurysmectomy (4).

the self-monitoring intervention group than in the usual care group (56% vs. 32%; p<0.001). the cumulative incidence of major bleeding at 6 months was 5.6% in the intervention group and 12% in the usual care group (p=0.0498; log-rank test). Recurrent thromboembolism occurred in 8.6% of patients in the intervention group and 13% in the usual care group (p=0.2). At 6 months, 13% of patients in the intervention group died; 16% of patients in the usual care group had died (p>0.2). The authors concluded that a comprehensive program of anticoagulation management including home monitoring reduced the frequency of major bleeding in older patients, was acceptable to most older patients to whom it was offered, did not require extensive training and could be implemented in a manner similar to the use of a home glucose monitor.

Khan, *et al*. (2004)(see section III.D.), reported the results of a randomized trial of 125 patients ages 65 years and older with atrial fibrillation who were taking warfarin for at least 12 months. Patients were randomized to either routine clinic care, education and clinic care, or education and self-monitoring and were followed for 6 months. Patients in the education and self-monitoring group showed a statistically significant improvement in percent-time in therapeutic range; changes in the education and clinic monitoring and routine clinic monitoring groups were not statistically significant. There was no association between age and percent time within range or between age and standard deviation of the INR measurement either before or after the intervention. Changes in percent time within range and standard deviation of INR also did not correlate with age.

Siebenhofer, *et al.* (2007), reported the results of a randomized trial of 195 patients aged 60 years or more who were receiving long-term oral anticoagulation therapy or who recently developed an indication for long-term anticoagulation but had not been on oral anticoagulation therapy. Patients were randomized to either the self-management group or the routine-care group. The patients in the self-management group underwent 4 training sessions and then had to measure their INR value with an absolute deviation of less than 0.4 from the reference value. If patients were not able to achieve this level of accuracy, then the training course was repeated. The percentage of time within target range and the percentage of INR measurements within target range were significantly higher (p<0.001 and p<0.001) in the self-management group versus the routine-care group within the first 6 months. The second 6 months showed similar results, p=0.029 and p<0.001, for percentage of time within target range and the percentage of INR measurements within target range in favor of the self-management group. The squared INR value deviations after 6 and 12 months were significantly lower in the self-management group (median 0.16 at both time points) compared to the routine-care group (median 0.25 at both time points)(p=0.0.035 and p=0.011 for the 6 and 12 month timepoints, respectively). The number of thromboembolic events requiring hospitalization, major bleeding events, and deaths were similar in both groups. The authors concluded that the results suggest self-management of oral anticoagulation is safe and feasible for elderly patients who are willing to participate in a structured training program. The trial is continuing and will follow patients from two to five years dependent upon when they enrolled in the trial.

Studies Analyzing Data with Regard to Age

Gadisseur, *et al.* (2003) conducted a randomized trial of 341 patients between the ages of 18 and 75 years old receiving long-term oral anticoagulation therapy. Patients were divided into 4 groups: (1) weekly management at an anticoagulation clinic where INR were measured by trained patients; (2) weekly patient self-management; (3) a routine care group of trained patients; (4) routine care group untrained in self-management. Linear regression analysis did not identify age as a predictive factor for time in range in a model containing age, sex, and type of coumarin.

Menéndez-Jándula, *et al.* 2005 (see Sections III.D and III.E.), conducted a randomized trial comparing self-management of oral anticoagulation therapy with clinic management in 737 patients with various indications for anticoagulant treatment. Mean ages (±SD, years) by treatment group and gender were:

	Patient Self Management	Conventional Management
Men	64±13	64±12
Women	65±15	67±11

Menédez-Jándula found no relationship between age and the percentage of INR tests within target range.

G. Conclusion

Substantial new clinical evidence supporting the use of home PT/INR monitoring has been published since the Medicare Decision Memorandum was published in September 2001. We identified 16 papers reporting results of 15 clinical studies published since 2000 that evaluate the effectiveness and safety of home PT/INR monitoring and include patients with underlying indications beyond mechanical heart valves alone. This evidence base supports a conclusion that home PT/INR monitoring is at least as effective and safe as in-clinic monitoring in maintaining INR levels within target range and reducing the incidence of major hemorrhagic and thromboembolic complications. Studies limited to patients with atrial fibrillation as well as those enrolling elderly patients support a determination that home PT/INR monitoring is effective and safe in these populations. In addition, analysis of studies by indication did not show that underlying reason for warfarin is associated with outcomes. Moreover, a broad range of additional studies included patients with conditions other than mechanical heart valves, including atrial fibrillation and deep vein thrombosis. In addition, analysis of studies by age did not show age as a predictor of outcome.

With respect to indication for warfarin, Heidinger, et al. observed: "All of these studies indicate that the success of self-management is not based on the indications for oral anticoagulation, but rather on the method itself, which yields a better outcome for all patients who are suitable candidates for self-management."[6]

With respect to age, the Oral Anticoagulation Monitoring Study Group authors observed: "Certain groups of patients, including elderly patients, nonambulatory patients, patients unable to drive, those who require intensive self-care, and younger patients for whom travel and work commitments make frequent attendance at a physician's office or anticoagulation clinic difficult, gain particular benefits from self-testing."[7] Menendez-Jandula, *et al.* also observed: "Many patients are candidates for self-management, since old age and low educational level do not seem to be major obstacles."[8]

IV. If the requestor has submitted an application to the FDA for market approval of the product for which coverage is sought, then a copy of the ''integrated summary of safety data'' and ''integrated summary of effectiveness data,'' or the combined ''summary of safety and effectiveness data,'' portions of the FDA application should be included in the request for an NCD. These documents will ensure that our review is comprehensive.

The test systems used to perform home PT/INR monitoring are classified as Class II medical devices (21 C.F.R. § 864.7750). Please see attached summaries from the 510(K) clearance notices for the three devices currently available commercially for home PT/INR monitoring (see Tab E): (1) Protime® Microcoagulation System manufacturerd by International Technidyne Corporation (K961835—cleared March12, 1997), (2) CoaguChek® PST System manufactured by Roche Diagnostics Corporation

[6] Heidinger, *et al.* (2000).
[7] Oral Anticoagulation Monitoring Study Group (2001).
[8] Menendez-Jandula, *et al.* (2005).

(K962571—cleared April 22, 1997), and (3) INRatio® manufactured by HemoSense Inc. (K021923—cleared October 24, 2002).

V. An explanation of the design, purpose, and method of using the item or equipment, including whether the item or equipment is for use by health care practitioners or patients.

Home PT/INR monitoring involves the furnishing, by a physician, IDTF or hospital clinic, of a PT/INR monitor (a prothrombin time test meter), test strips to run in the monitor, lancets for collecting blood samples, and alcohol swabs (for preparing the skin) for the self-testing of prothrombin time by patients or their caregivers at home (or otherwise outside the physician's office setting). The devices are furnished only on the prescription of a physician and only following appropriate training on the use of the devices (including demonstration that the patient or caregiver can perform testing).

VI. A statement from the requestor containing the following:

- ***An explanation of the relevance of the evidence selected.***

The 2001 Decision Memorandum was based upon an assessment of the published clinical evidence as of 2001. At that time, most controlled trials evaluating the effectiveness and safety of home PT/INR monitoring involved patients with mechanical heart valves as the underlying condition for warfarin therapy. For this reconsideration request, we conducted an assessment of the published literature since 2001 on home PT/INR monitoring but excluded those papers reporting studies that were limited to patients with mechanical heart valves. We also identified two papers, published in 2000, that were not included in the previous Decision Memorandum and which provided evidence on the effectiveness and safety of home PT/INR monitoring in the elderly and in patients with atrial fibrillation and deep vein thrombosis. We also included the findings from a meta-analysis of 14 trials that was published in *The Lancet* this year. The meta-analysis showed significant benefits of home PT/INR monitoring with respect to hemorrhagic events, thromboembolic events and death—significant findings that were generally not observed in the individual trials due to small numbers.

- ***Rationale for how the evidence selected demonstrates the medical benefits for the target Medicare population.***

The outcome measures in the studies presented in this reconsideration request include measures of anticoagulation control, including percent time in target range and percent of INR values in target range. In addition, many studies reported on clinical outcomes, including thromboembolic events, hemorrhagic events and death. The selection of time in therapeutic range as a relevant endpoint for many of the trials is supported by the 2001 Decision Memorandum that provided the basis for Medicare coverage of home PT/INR monitoring: *"In this situation, TTR does seem to be an adequate and acceptable surrogate. Of note, the Managing Anticoagulation Service Trial (MAST), a RCT comparing anticoagulation services to usual care, has used TTR as its primary outcome, a design which was approved by an external review panel of the Agency for Health Care Research and Quality (AHRQ). In a recently published literature review, 'Relationship between test frequency and outcomes of anticoagulation: a literature review and commentary with implications for the design of randomized trials of patient self-management' by Samsa and Matchar, the authors note that nearly 20 studies, some large, well-designed clinical trials have demonstrated that increased TTR leads to a reduction in thromboembolic and hemorrhagic events.*[9] . . .

[9] Samsa GP, and Matchar DB. Relationship between test frequency and outcomes of anticoagulation: a literature review and commentary with implications for the design of randomized trials of patient self-management. *Journal of Thrombosis and Thrombolysis* 2000;9:283-292.

The authors conclude that 'there is a strong relationship between TTR and event rate that is supported by a large literature.'"

The underlying studies which Samsa and Matchar reviewed comprised 15 studies of which 6 were in patients with atrial fibrillation, 5 were in patients with various indications for anticoagulation, 1 was in patients post-myocardial infarction, 1 was in patients post-hip replacement; only 2 studies were limited to patients with mechanical heart valves. Therefore, the determination that TTR is an appropriate endpoint to support coverage for home PT/INR monitoring should apply as strongly in the context of this reconsideration request as it did with the initial decision to provide coverage for patients with mechanical heart valves.

Several of the papers which Samsa and Matchar reviewed for their analysis included elderly populations and several included analyses investigating whether age is or is not a predictor of risk for an adverse event. Therefore, Samsa and Matchar's findings about the relationship between TTR and events should apply to the elderly. In any event, the 2001 Decision Memorandum accepted the Samsa and Matchar analysis supporting use of TTR as an outcome measure relevant to the Medicare population and supporting coverage for home PT/INR monitoring.

- ***Information that examines the magnitude of the medical benefit.***

As noted above, the outcome measures in the studies presented in this reconsideration request include well-established measures of anticoagulation control, such as percent time in therapeutic range and clinical outcome measures, including major hemorrhagic events, major thromboembolic events, and death.

- ***Reasoning for how coverage of the item or service will help improve the medical benefit to the target population.***

The current National Coverage Determination for home PT/INR monitoring is limited to patients with mechanical heart valves. Many patients who require long-term warfarin anticoagulation therapy have other underlying conditions, such as atrial fibrillation and deep vein thrombosis. Suitably selected and properly trained patients with atrial fibrillation, deep vein thrombosis, or other underlying conditions for long-term warfarin therapy can benefit from access to home PT/INR monitoring. Representatives from several clinics have indicated to us that they would be more likely to adopt home PT/INR monitoring if coverage were extended to a broader segment of their clinic population. As noted above (see Section III.A.), the limited scope of the current benefit means the clinics must undertake substantial time and expense to set up systems for home monitoring and reporting for a very small pool of patients (the revenues would not be sufficient to support the expense). More importantly, when they evaluate patients for home monitoring, their assessment is based upon need for frequent monitoring and the ability and interest of patients (or their caregivers) to perform home monitoring. Their assessment is unrelated to the underlying condition for which warfarin is prescribed, and they have indicated to us their interest in offering the service to suitable candidates without limiting it to patients with mechanical heart valves.

- ***In the case of an aggrieved party, how that party is ''in need'' of the item or service.***

Not applicable.

VII. A description of any clinical trials or studies currently underway that might be relevant to a decision regarding coverage of the item or service.

The Home INR Study (THINRS) is a study in a Veterans' Affairs population with mechanical heart valves (MHV) and/or atrial fibrillation comparing weekly home PT/INR monitoring with 4 weekly monitorings in an anticoagulation clinic. The study is ongoing (see attached study design paper Tab F).

VIII. Information involving the use of a drug or device subject to FDA regulation as well as the status of current FDA regulatory review of the drug or device involved. An FDA regulated article would include the labeling submitted to the FDA or approved by the FDA for that article, together with an indication of whether the article for which a review is being requested is covered under the labeled indication(s). (We recognize that the labeling on FDA-approved products sometimes changes. For purposes of our review, we are interested in the labeled indications at the time a requestor submits a formal request. If, during our review, the labeled indication or status of a pending FDA approval or clearance changes, we expect the requestor to notify us.)

The test systems used to perform home PT/INR monitoring are classified as Class II medical devices (21 C.F.R. § 864.7750). Please see attached summaries from the 510(K) clearance notices for the three devices currently available commercially for home PT/INR monitoring (see Tab E): (1) Protime® Microcoagulation System manufacturerd by International Technidyne Corporation (K961835—cleared March12, 1997), (2) CoaguChek® PST System manufactured by Roche Diagnostics Corporation (K962571—cleared April 22, 1997), and (3) INRatio® manufactured by HemoSense Inc. (K021923—cleared October 24, 2002).

The expansion of coverage for home PT/INR monitoring sought by this reconsideration request is fully within current product labeling for the home PT/INR monitoring systems. The package labeling for these systems has no limitation based upon the underlying condition for which warfarin is prescribed.

IX. In the case of items that are eligible for a 510(k) clearance by the FDA, identification of the predicate device to which the item is claimed to be substantially equivalent.

The devices used to perform home PT/INR monitoring were cleared under 510(K) notice to the FDA by reference to cleared professional use PT monitoring systems as the predicate devices. (See attached summaries from the 510(K) notices for each of the three devices currently available commercially in the US for home PT/INR monitoring—Tab E).