Decision Memo for Prothrombin Time (INR) Monitor for Home Anticoagulation Management (CAG-00087N)

Decision Summary

The studies reviewed demonstrated that home prothrombin monitoring significantly improve time in therapeutic range for select groups of patients, compared to testing done in physician offices, or anticoagulation clinics. Increased TTR leads to improved clinical outcomes, with reductions in thromboembolic and hemorrhagic events. The body of evidence is suggestive, but notable weaknesses, as described earlier, still exist.

At this point in time, we are announcing our intention to issue a national coverage decision covering home prothrombin monitoring with the use of these devices for patients with mechanical heart valves, since these patients have a unique need, and they were the patients primarily studied. It is unclear if other patient populations are as likely to benefit. In addition, patients should have been anticoagulated for at least three months prior to use of the device and should undergo an educational program on anticoagulation management and the use of this device. Self-testing with the use of the devices should not occur more frequently than once a week.

Consistent with the mandates of section 4554 (b) (1) of the Balance Budget Act, the NCD for INR monitoring cannot be effective until after the Secretary has first adopted national coverage and administrative policies for clinical diagnostic laboratory tests. Thus, the agency will issue a national coverage decision covering INR monitoring once the Secretary has adopted such policies.

We are interested in reviewing data on other indications as it becomes available. We welcome interested parties to come to CMS to discuss appropriate study design and outcome measures.

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Decision Memo

This decision memorandum does not constitute a national coverage determination (NCD). It states CMS's intent to issue an NCD. Prior to any new or modified policy taking effect, CMS must first issue a manual instruction giving specific directions to our claims-processing contractors. That manual issuance, which includes an effective date, is the NCD. If appropriate, the Agency must also change billing and claims processing systems and issue related instructions to allow for payment. The NCD will be published in the Medicare Coverage Issues Manual. Policy changes become effective as of the date listed in the transmittal that announces the Coverage Issues Manual revision.

To: Administrative File: CAG-00087A
Home Prothrombin Time (INR) Monitor for Anticoagulation Management

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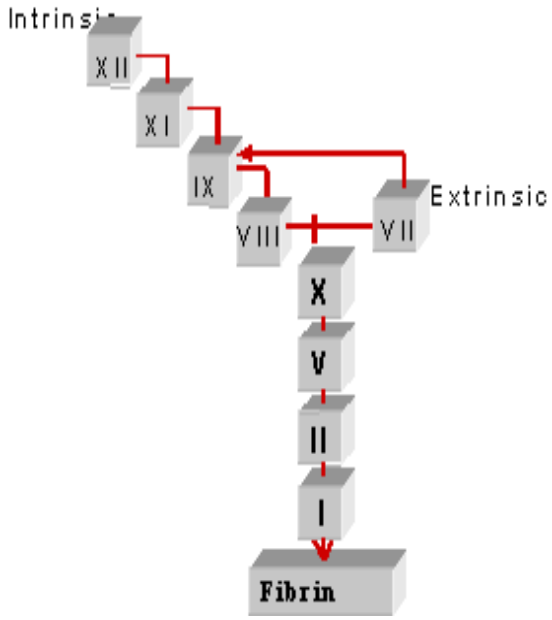
This memorandum serves five purposes: (1) provides a brief outline of the coagulation cascade and indications for anticoagulation (2) describes the various methods of monitoring anticoagulation with an emphasis upon home prothrombin time (INR) monitors, (3) reviews the history of Medicare's policies regarding INR monitors; (4) analyzes relevant scientific and clinical literature on the use of INR monitors for patients being anticoagulated; and (5) delineates the reasoning for announcing our intention to issue a positive national coverage decision relating to home prothrombin (INR) monitoring for patients with mechanical heart valves.

Clinical Background



There are two converging pathways of coagulation: (1) instrinic and (2) extrinsic. The intrinsic pathway begins with surface activation of coagulation proteins, while the extrinsic pathway begins with the exposure of blood to tissue thromboplastin. The partial thromboplastin time (PTT) screens the intrinsic limb while the prothrombin time (PT) screens the extrinsic or tissue-factor dependent pathway. Both tests evaluate the common coagulation pathway. Although both tests are useful in determining appropriate anticoagulation for various indications, this decision memorandum only addresses those conditions which require prothrombin measurements.

Prothrombin time (PT)
Since commercial thromboplastins have different potencies and markedly affect the resulting PT, the International Normalized Ratio (INR) method was developed. In this method, the ratio of the patient's PT is compared to the mean PT for a group of normal individuals. The ratio is adjusted for the sensitivity of the laboratory's thromboplastin determined by the International Sensitivity Index (ISI). The INR = (PT patient / PT normal) ^{ISI}. Use of the INR permits physicians to obtain the appropriate level of anticoagulation independent of laboratory reagents. PT is used for patients on warfarin therapy since warfarin affects the vitamin K-dependent factors measured by PT.

Indications for Oral Anticoagulation Therapy

According to the American College of Chest Physicians Consensus Conference on Antithrombotic Therapy, there are at least ten indications for oral anticoagulation therapy.

Table 1: Indications for Anticoagulation[1]

Mechanical prosthetic heart valves (high risk) Prophylaxis of venous thrombosis (high risk surgery) Treatment of venous thrombosis

Bileaflet mechanical valve in aortic position Treatment of pulmonary embolism Prevention of systemic embolism Tissue heart valves (first 3 months) Acute myocardial infarction (to prevent systemic embolism, or recurrence) Valvular heart disease Atrial fibrillation

The most common and universally agreed upon indications for warfarin, are patients with mechanical valves, and to a lesser extent, those patients with atrial fibrillation who are post-cerebrovascular accident or transient ischemic attack. Other indications include atrial fibrillation with thromboembolic risk factors including age over 65 years, diabetes, hypertension, as well as congestive heart failure. Selected patients at high risk (e.g. individuals with mechanical heart valves) are recommended to have a higher therapeutic INR range. There are short-term indications for anticoagulation such as treatment of pulmonary embolus; however, this document primarily addresses the use of this device for chronic anticoagulation.

Proper anticoagulation remains a significant problem for Medicare beneficiaries. There are patients that are not adequately anticoagulated (over or under- anticoagulated), as well as a large number of patients who have an indication for anticoagulation but are not on anticoagulants due to perceived contraindications, or physician misinformation/safety concerns. This inadequate anticoagulation can have significant health effects, most notably increased risk of stroke, and myocardial injury, as well as bleeding and clot formation.

Underutilization

Despite numerous guidelines recommending anticoagulation for several indications, as well as a quality parameter of CMS's Peer Review Organizations, thousands of patients are not being anticoagulated. As Table 2 demonstrates, although 100% of patients with mechanical valves are anticoagulated, less than 60% of patients with atrial fibrillation receive warfarin, and less than 20% of patients post-stroke are being anticoagulated.

Table 2: Anticoagulation - Indications and Utilization[2]

Primary Indication	US Population (`000s)	Warfarin Utilization
Mechanical Heart Valve	400	100%
Atrial Fibrillation	2,000	60%

Primary Indication	US Population (`000s)	Warfarin Utilization
Post-stroke	300	21%

This underutilization disproportionately affects Medicare beneficiaries since most patients needing to be anticoagulated are Medicare patients. For instance, the incidence of atrial fibrillation increases as one gets older, from approximately 0.5% for ages 50-59, to nearly 10% for ages 80-89.[3]

There are numerous reasons why patients are not being anticoagulated.[4] [5] Although several guidelines and consensus conference reports have been issued, there is still a knowledge deficiency on the part of many physicians as to the appropriate indications and relative contraindications. Given the narrow therapeutic index of warfarin, many physicians are fearful of anticoagulation, and are often reluctant to place patients, especially elderly patients on an anticoagulation regimen.

Frequency of Testing

In general, most patients on chronic warfarin are tested approximately once a month. Recent data demonstrates that this frequency is inadequate for the majority of patients. The general recommendation for warfarin monitoring to be performed once every 4-6 weeks is not based on pharmacokinetics nor clotting factor half lives but rather by practical constraints of access and labor-intensiveness balanced against complications.

Warfarin affects the vitamin-K dependent clotting factors. There are numerous factors that affect the bioavailability of warfarin, such as inconsistent dietary vitamin K intake, changes in drugs that cause drug/drug interaction, and variable binding to plasma proteins.[6] As a result, treatment of each anticoagulation therapy patient can be highly individualized. This variability necessitates frequent testing.

As noted earlier, warfarin has a narrow therapeutic index.[7] Oral anticoagulant therapy has a minor bleeding complication rate of 10-20%, and major bleeding episodes in 1-5% of cases. Too much warfarin can have serious effects as demonstrated. Numerous studies in the literature demonstrate that INR > 3 results in higher risk of serious hemorrhage. An INR of 4 nearly doubles the risk, and an INR of 6 increases one's risk of developing a serious bleed nearly 7 times that of someone below an INR of 3.

Of comparable concern is underanticoagulation. Inadequate dosage can also lead to serious consequences. Numerous studies, including Hylek et al, demonstrated that INR below 2.0 results in a higher risk of strokes. This risk increases rapidly as INR drops below this threshold.

Monitoring Anticoagulation

There are at least three sites/methods of monitoring anticoagulation:

1. Physician Offices
2. Anticoagulation Clinics [8]
3. Home Prothrombin (INR) Monitors

Nearly eighty percent of patients being anticoagulated are managed through physician offices, the "usual care" approach. Individual physicians manage their patients, and test frequency is generally once every 4-6 weeks. This method has the highest adverse event rate, at > 15%. Approximately 20% of patients receive their care through an anticoagulation service, comprised of nurses, physicians, and a pharmacist. Test frequency is approximately once every 2-3 weeks, with an adverse event rate of < 8%. Patient self-testing/self management through the use of a home prothrombin monitor is another method of monitoring anticoagulation, and presently represents < 5% of patients being anticoagulated.

FDA Approval/Clearance

Home prothrombin monitors have been cleared by the FDA under a 510 (k) process. A 510(k) is a premarketing submission made to FDA to demonstrate that the device to be marketed is as safe and effective, that is, substantially equivalent, to a legally marketed device that is not subject to premarket approval (PMA). Typically, no clinical data is required as part of the 510 (k) application, but instead the clearance process focuses on technical performance. For these devices, however, the FDA granted clearance based upon data demonstrating that properly selected and trained patients, or the caregivers, can generate INR test results comparable to laboratory instruments. These devices must be prescribed by a physician. The PT measured by these devices are granted waived status under the Clinical Laboratory Improvement Act. [9]

There are currently 4 FDA approved 510(k) devices for use in the home on the market used to indicate clotting activity of blood and to monitor the status of oral anticoagulant therapy. The predicate for the 510 (k) devices were the same named devices for professional use. The 510 (k) approval was granted to take the devices to the home. All products have as part of their label that the physician is responsible for the selection, training and ongoing management of patients selected for home testing.

3/12/97 Protime Microcoagulation System by International Technidyne Corp.

4/22/97 Coaguchek PST System by Boehringer Mannheim Corp (The company has since become Roche Diagnostic). Of note, the labeling content differs from the predicate device in that it is intended for patient rewritten to 7th grade reading level or lower. Additional labeling created to assist professionals with suitable selection and proper training of patients.

9/30/98 Avocet by Avocet Medical Incorporated.

5/15/01 Rubicon Prothrombin Time Monitoring System by Lifescan, a Johnson and Johnson company

An example of the 510 (k) submission (Avocet's submission) includes the following:

1.) 150 patients were enrolled at 6 sites for a 10 week longitudinal study
2.) Patients were selected at random with demographics to ensure broad representation.
3.) Patients were trained on the use of the system
4.) Once trained, patients were given a meter and supplies and instructed to test twice per week for 10 weeks and record their results in a log book.
5.) Every other week (every 4th test) the subject would return to the lab and perform the following activities:

a.) Test in the presence of the Health Care Professional (HCP).
b.) The HCP would then also perform a test on the patient using the same meter
c.) At each visit the HCP and patient would alternate performing the test in duplicate
d.) A venous blood draw would be taken and testing performed on an >MLA-800 (the lab reference device)
e.) The log book was copied and the meter memory was downloaded
6.) Results were then calculated for the following: a.) Accuracy of patients vs. the central lab MLA-800 reference
b.) Accuracy of professional vs. the central lab MLA-800 reference
c.) Accuracy of the professional vs. the patient
e.) Precision of the patients duplicate testing
f.) Precision of the professionals duplicate testing
g.) Clinical agreement was assessed between all 3 sources (patient, professional and MLA reference)
h.) Comparison of the patient's log-book vs. the data downloaded from the meter was also assessed to determine the influence of any possible transcription errors.

History of the Medicare Coverage Process and Timeline of Recent Activities

Currently, Medicare does not have a national coverage policy with regard to the use of home monitoring of prothrombin time. The four Durable Medical Equipment Regional Carriers (DMERCs) currently do not cover these devices, denying claims as not being "medically necessary and reasonable."

A committee of CMS physicians, physician representatives of other federal agencies, and some Contractor Medical Directors considered this equipment for a national coverage decision in May 1997. This committee identified two major concerns regarding home monitoring of anticoagulant therapy: (1) What action would the patient take following determination of the prothrombin time and ; (2) would the use of such a device improve anti-coagulation control? After reviewing seven articles (Bernardo, Hasenkam, White, Cannegieter, Hylek, Levine, Hirsh) the committee recommended against Medicare coverage based on their concerns that: (1) the data did not conclusively show improved control of anti-coagulation therapy, (2) use of the device might increase risk in noncompliant or careless patients, and (3) the device might limit access to regular physician oversight. In making the noncoverage recommendation, the committee noted:

- The home prothrombin test does not resemble the home glucose monitor in that the patient does not take any direct action;
- Patients can easily obtain the test from a local testing center or from their physician's office, and patients will have to contact their physicians anyway;
- Concern about the device's continued accuracy over time;
- Historic poor compliance and sporadic use of DME by patients.

The committee's recommendation for national noncoverage was never executed, and carrier discretion has prevailed. [10]The DMERCs have decided not to cover these devices, based on their belief that these devices are not medically necessary and reasonable. [11] There are certain conditions under which a home health agency may test prothrombin time at home, but the need for a prothromin test cannot be an indication for a home health visit.

Several manufacturers of these devices have met with CMS on numerous occasions to discuss the possibility of limited coverage. These manufacturers believe that the use of this device will improve time in therapeutic range, as well as decrease thromboembolic and hemorrhagic events. The American College of Cardiology, the American Academy of Neurology, the Society of Thoracic Surgeons have written to the agency advocating for some type of coverage.

Timeline of Recent Activities

July 11, 2000	Met with representatives of the Patient Self-Testing Coalition (a group made of 5 leading manufactures of the home prothrombin (INR) monitors. The Coalition was organized/coordinated by Patton Boggs, LLP.
August 4, 2000	Additional meeting with representative of the Patient Self-Testing (PST) coalition.
October 26, 2000	Meeting with Lifescan, a Johnson and Johnson company, manufacturer of the device, to discuss scientific studies
February 27, 2001	Representatives from St. Jude Medical, Inc presented data to show how PST can improve anticoagulation therapy for medical heart valve patient outcomes.
March 12, 2001	Benefit category determination made by Centers for Medicare Management. It has been designated as Diagnostic Services, as set forth in Section 1861 (s) (3) of the Social Security Act. With respect to waived diagnostic services, the regulations at 42 CFR 493.15 stated that waived laboratory tests are simple laboratory examinations and procedures which are cleared by the FDA for home use; employ methodologies that are so simple and accurate as to render the likelihood of erroneous results negligible; or pose no reasonable risk of harm to the patient if the test if performed incorrectly.

Summary of Evidence

In reviewing the literature, we decided to ask the following questions:

1. Is the use of home INR monitor for testing PT at least equivalent to lab testing such as an coagulation clinic/physician office testing with respect to: (a) time in therapeutic range (TTR) and/or (b) incidence of thromboembolic events and/or (c) hemorrhagic events?
2. Is there evidence that self-testing and/or self-management is at least equivalent to self-testing alone for the above three outcomes?

In determining the articles which would be eligible for review, we used the following inclusion and exclusion criteria:

Inclusion Criteria

1. Articles must be published in English language
2. Study must have been on human subjects
3. Articles must have been published in a peer-reviewed journal from 1989-2001
4. Study must have included a control group not using the home INR monitors
5. Study must have looked at one of the following outcome measures:

   Primary: 1. Thromboembolic events
   2. Hemorrhagic events

   Secondary: 1. Time in therapeutic range

Exclusion Criteria

1. Editorials
2. Abstracts
3. Review Articles
4. Letters/Comments

Based on a combination of the following search terms and the aforementioned inclusion/exclusion criteria, 11 articles were obtained.

Prothrombin time	International Normalized Ratio

Anticoagulation	Anticoagulants
Anticoagulation clinics	Anticoagulation monitoring
Prothrombin time monitoring	Point of care systems
Point of care prothrombin time	Coagulation tests
Anticoagulation - complications	Anticoagulation - adverse events
Warfarin	Warfarin monitoring
Atrial fibrillation	Atrial fibrillation - treatment
Atrial fibrillation - complications	Stroke
Heart valve prosthesis	Heart valve prosthesis - complications

These 11 articles included the following study types:

- 7 Randomized Controlled Trials
- 2 Cohorts
- 2 Case Controls

A detailed analysis of each article can be found in Appendix A. The following represents a brief summary of the studies.

White (1989) evaluated the efficacy and accuracy of home prothrombin monitors for patients initiating warfarin therapy. In a randomized clinical trial, the authors assigned 50 patients being discharged from a hospital who required anticoagulation to either home monitoring (managed by a general internist) or an anticoagulation clinic. (Indications for anticoagulation included DVT, mechanical heart valves, and arterial thromboembolism. In addition, they only included those patients whose prothrombin time had been unstable prior to discharge) The primary endpoint was the percentage of time PT remained within therapeutic range. After 8 weeks, 46 patients completed the study. As Table 3 demonstrates, patients using the home monitor had less variation in their INR, resulting in greater time in therapeutic range. There were no significant adverse events.

Table 3: Percentage of INR in Therapeutic Range: (White, 1989)

	Home Monitor	Clinic Monitor

Number of Patients	23	23
% Therapeutic Range	87	68 (p<0.001)
% Above Range	6.7	9 (p =NS)
% Below Range	6.3	23 (p<0.001)
Major Hemorrhage/Thrombosis	0	0
Total Number of Tests	427	190

Ansell (1995) analyzed data in a retrospective cohort, coupled with a prospective trial, trying to determine the ability, safety, and efficacy of patients to self-monitor and self-adjust their warfarin dose with the use of a home prothrombin monitor. He looked at 20 patients using the home monitor and then matched these results with 20 controls receiving anticoagulation at an academic medical center. Patients were those on chronic warfarin therapy for more than seven years. They were chosen based on the investigator's assessment of their compliance stability, and ability to follow directions. 23 patients studied had mechanical valves, 10 had venous thromboembolism, 2 had TIA's, 2 had myocardial infarctions, 2 cardiomyopathy, 1 homocysteinuria. Patients were given a standard algorithm to follow, which allowed them to self-manage doses the majority of the time. (Teaching was done by an anticoagulation nurse specialist over a 2 week period) The major outcomes were percentage of PTs within the therapeutic range, ability of patients to make correct dosage-adjustment NCDs, and occurrence of hemorrhagic and thrombotic events. Mean follow-up was 44 months. As Table 4 shows, subjects using the home monitor and who self-adjusted their medication based on the home INR values had PT in range 88.5% of the time versus 66% for the controls. The self-managed patients also had fewer dose changes. There were no significant differences in thromboembolic/hemorrhagic events. In addition, 98% of patients stated that they preferred self-management over routine anticoagulation clinic management.

Table 4: PT testing and Dose Changes (Ansell, 1995)

	PST/self management	*Controls*	*P value*
# of patients	20	20	
Study duration	44.7 months	42.5 months	>0.10
PT testing interval	13.8 days	16.0 days	>0.10
Total PT's	2153	1608	>0.05
PT above range (%)	5.2	10.3	<0.001
PT below range (%)	6.3	21.8	<0.001
PTs in range (%)	88.5	66	<0.001
Dose changes	11.5	22.7	<0.001

Hasenkam (1995) evaluated 21 patients who were admitted for open heart surgery and had indications for lifelong anticoagulation. Patients were studied for at least 9 months, with the use of a home device. Twenty matched-controls were extracted. Median value for all INR measurements were within therapeutic range for those using a home INR device 100% of the time; for the matched controls, it was 70%. There were no major bleeds in either group; one patient may have had a transient episode of blurred vision due to a small embolus in the experimental group.

Horstkotte (1996) conducted one of the first randomized prospective trials related to home INR testing. He examined outcomes of patients with mechanical valves between those that self-tested and self-managed with a home device, versus those that underwent laboratory testing by their physicians. Home INR patients tested once every 4 days versus once every 19 days in the usual care group. At the conclusion of the study, the authors determined that patients using the home INR device and who self-managed were more often in therapeutic range, and had fewer bleeding/thromboembolic events, although reduction in events was not statistically significant. The home testing patients also demonstrated a high degree of compliance with the testing schedule and treatment algorithm.

Table 5: Patients with Mechanical Valves/ UC vs PST (Horstkotte, 1996)

	Usual Care	*PST/self management*
Number	75	75
Mean INR	3.9 +/ 1.3	3.7 +/0.3
Mean Test Interval	18.9	3.9
INR Range (%)	58.8	92.4**
Thromboembolic events (%	3.6%	0.9%
Bleeds	10.9%	4.5%

** p<0.001

Sawicki (1999) investigated the effects of self-management on patients receiving anticoagulation. In a randomized, single-blinded, multicenter trial, the author randomized 179 patients (151 patients with mechanical heart valves) to either an anticoagulation self-management group based on a structured teaching and treatment program (lasting 3-5 hours per patient), or conventional care provided by family physicians, including referral to specialists. 92% were followed for 6 month (83 in the self-management, 82 in the control group). The main outcome measure was deviation of INR values from the individual INR target range (squared). As Table 6 notes, patients in the self-testing and self-management group had a INR in the therapeutic range 1.5 times more often than the usual care group; there was also a significant reduction in the % of INR below range. Treatment-related quality-of-life measures (general treatment satisfaction, self-efficacy) were significantly higher in the intervention group compared with controls. Limited information was provided on the process of care in the controls.

Table 6: Time in Therapeutic Range (Sawicki, 1999)

	Usual Care	*PST/self-management*
Number of patients	89	90
In Range (%)	34	57*
Below Range (%)	50	33**
Above Range (%)	16	10
Hemorrhagic events	1	1
Thrombotic events	0	2

* p=0.006
** p=0.03

Beyth (2000) conducted a randomized clinical trial of 325 patients with a variety of indications for anticoagulation. Patients had been receiving warfarin for at least 10 days and then they were randomized to be tested either in physician offices or at home, and were followed for six months. Using an intent-to-treat analysis, the authors showed a lower rate of major hemorrhage in the PST group (5.7%) than in the physician offices group (12%) p=0.049. Patients using the home device demonstrated 56% TTR vs 32% TTR for the physician office group p<0.001

Cromheecke (2000) evaluated 50 patients on long-term oral anticoagulant treatment in a randomized controlled crossover study. Patients were self-managed, or were managed by an anticoagulation clinic for a period of three months. After this period, the alternative strategy was followed. INR was measured every 1-2 weeks. Indications were prosthetic heart valves (46%), atrial fibrillation (24%), and familial thrombophilia (30%). All patients underwent a structured educational program of two, 2-hour sessions. Primary endpoint was number of measurements within therapeutic range. Secondary endpoints included the % of TTR, number of patients who were in the therapeutic range for 0-100% of the time, and the number of patients who achieved a better control of anticoagulation during one of the two management strategies. As Table 7 reveals, at the end of the study, the authors found that self-management of INR resulted in anticoagulation control that was equivalent, or slightly better than anticoagulation clinics. Patient satisfaction was also markedly superior with the use of the home device.

Table 7: Self Testing/Self Management vs Anticoagulation Clinic (Cromheecke, 2000)

	Self testing/Self management	*Anticoagulation Clinic*
Frequency of Testing	8.6 days	9.0 days
TTR (+/- 0.5)	55%	49% *
50% time TTR	60%	52%
75% time TTR	27%	12%
INR < 1.5, or > 5.0	3.5%	5.3% **

*p=0.06
** p=0.07

Watzke (2000) compared weekly self-testing and self-dosing with standard management. In a prospective clinical trial, he enrolled 49 patients in the self-testing group, and 53 patients in the standard management group. Only patients with stable anticoagulation were included in the study. Patients included those with mechanical heart valves or patients with atrial fibrillation, or venous thromboembolism, and were either high-intensity or low-intensity. Patients were followed for one year. Self-managed patients tested weekly, while standard management patients tested every 4-8 weeks. As Table 8 documents, patients in the self-management arm were in therapeutic range more often than patients allocated to the usual care group. In addition, the mean-square deviation was nearly double in the usual care group compared to the PST group. The individual INR-deviations were dependent on the type of management in a generalized linear model.

Table 8: Time in Therapeutic Range (Watzke, 2000)

	Usual Care	*PST/self-management*

Number of patients	53	49
Therapeutic range (%) (overall)	73.8	84.5
High intensity (2.5-4.5) (%)	80.1	86.2
Low intensity (2-3) (%)	68.9	82.2

ESCAT (Early Self Controlled Anticoagulation Trial) was started in February 1994 and concluded in October, 1997. It was a randomized prospective trial of 1200 patients who received mechanical heart valves; half used patient self-testing and management with a home device, and half were treated and controlled conventionally by a physician. The study was designed to answer the following questions:

- Does patient self-management lead to an improved adherence to the therapeutic range, taking quality of life into account?
- Does INR self-monitoring by the patient reduce the complication rate following mechanical heart valve replacement, and thus morbidity and mortality?
- Does INR self-monitoring justify low-dose anticoagulant therapy following mechanical cardiac valve replacement?

Koertke (2000) looked at the first 600 patients who completed followup of at least 2 years, with the observation period ranging from 25 to 51 months. 295 patients were part of the conventional treatment group; 305 patients were in the INR self-management group. The self-management group was trained 6-11 days after surgery. Patients who did self-testing and self-management in the home had INR in therapeutic range 78.3% of the time, versus 60.5% in the conventional group ($p<0.001$). Only 18.8% of the time was INR < 2.5 in the self-management group, versus 35.8% for the conventional group ($p<0.001$). Of note, after 8 weeks, the self-testing/self-management group remained in target INR range for the entire observation period. The authors also evaluated complications on a 4 grade scale.[12] 9.5% of patients in the self-management group had a Grade III complication versus 15.3% in the conventional treatment group ($p< 0.05$). The authors suggest that the rate of thromboembolism could be decreased from 2.1% to 1.2%.

The German Experience with Low Intensity Anticoagulation (GELIA) was a randomized, multicenter, prospective controlled trial with three anticoagulation intensity regimens for patients with aortic and/or mitral bileaflet prostheses. By June 30, 2000, a total of 2735 patients over 7 years had been studied. Patients were either managed by a general practitioner or self-management. Since self-management was initially not widespread at the beginning of the study, the subgroup of patients who changed from general practitioner management to self-management served as their own control. TTR and incidence of serious complications were measured. Of the 2735 patients, 600 used self-management. 278 patients served as their own control. TTR was 62.5% for the general practitioner method, versus 73.5% for the self-management method. The difference was statistically significant ($p<0.001$) The incidence of serious complications (bleeding and TE's Grade II and III) was 30% lower in the self-management group, although the difference was not statistically significant.

Position Statements

In general, official guidelines from specialty societies, derived from an evidence-based process, are sought and considered as part of the coverage process. Although there are no official guidelines from specialty societies relating to the use of home INR monitors, the American Academy of Neurology (AAN), the American College of Cardiology (ACC), and the Society of Thoracic Surgeons/American Association for Thoracic Surgery (STS/AATS) wrote to the Agency advocating coverage. Such letters are not weighed as heavily as official guidelines or statements derived from an evidence-based process, but still are considered as part of the evidence reviewed. It is important to determine the interest and perspective of the clinical community, which at times can be slightly different than the research community.

In a July 11,2000 letter, Francis Kittredge, MD AAN President writes:

"Recent scientific presentations and publications offer evidence that access to frequent PT testing serves to optimize time in therapeutic range and thereby improve patient outcomes. We believe this benefit would improve patient care if PST was extended as a treatment option... The American Academy of Neurology realizes that home testing requires close communication with patients, and recognizes the improved outcomes and reduction in adverse events that can occur with home testing."

The ACC has written to the agency numerous times over the past four years. In its most recent March 19, 2001 letter, Douglas Zipes, ACC President writes:

"The ACC believes that these devices should be covered...when a qualified physician recommends their use for patient...The ACC finds physicians choose to recommend these devices for patients who need anticoagulation monitoring and are both able to use the devices properly and able to carry out self-monitoring protocols. The physicians counsel their patients on how the patients should adjust the anticoagulant dosage depending on the results of the test in general. There are a set of test values within which the patient can vary the dose of medication by prearranged algorithm for optimal therapeutic benefit. Also, physicians instruct the patients to contact their offices when the test values are markedly abnormal or when there are specific questions beyond self-management...."

In a May 15, 2001 letter, STS/AATS commented to CMS that "..the societies support coverage of home prothrombin time (INR) monitoring for anticoagulation management"

"The STS/AATS support coverage for the following reasons:

- The safety and effectiveness of warfarin therapy is optimized when INR values are properly maintained within a target therapeutic range. As the distance from a target INR value increases or decreases, the likelihood of adverse events also increases, thus maintaining a therapeutic range is vital for patient well-being.
- Patient self-testing for mechanical heart valve patients would improve patient outcomes. The cost of complications from mechanical heart valve patients is high and may require additional surgical intervention and hospitalization cost to replace a thrombosed valve or treat a bleeding event.
- Studies have shown that by empowering warfarin patients to perform PT-INR self-testing, more patients spend a higher proportion of time within their target INR range leading to fewer adverse effects."

CMS Analysis

In determining whether home INR monitors are "medically necessary and reasonable" services, the following analytic questions arise:

1. Is the use of home INR monitor for testing PT at least equivalent to lab testing/physician office testing with respect to time in therapeutic range (TTR)?
2. Is the use of home INR monitor for testing PT at least equivalent to lab testing/physician office testing with respect to incidence of thromboembolic events and/or hemorrhagic events?
3. Given that the incidence of thromboembolic and/or hemorrhagic events are small, and some studies may be underpowered to detect a difference in incidence amongst various management methods, is TTR an adequate surrogate for reduction in thromboembolic/hemorrhagic events?
4. Who is the appropriate patient population?

There is a significant body of scientific and clinical literature to answer these questions. (See Table 9) As noted earlier in this document as well as Appendix A, there are over 11 studies, with over 2000 patients. The majority of studies were fairly well-designed randomized clinical trials, with most patients self-testing and self-managing. Self-management represents a continuum - it could represent patients that self-test, and then simply call the doctor with the results, or it could represent patients that self-test, and then have a set algorithm that they use to make adjustments to their warfarin dose within certain parameters. It is only when they exceed such parameters that they call their doctor. It is important to note that in such a setting, even when patients do not make adjustments, they are still self-managing. For the purposes of this decision memorandum, we consider patient self-management to primarily involve dosage adjustments in an algorithm approved by a patient's treating physician.

Table 9: Brief Summary of Studies

Author, Year	Indications MHV AF other	# of patients	Age Mean	PST PSM	Type of Study	Results
White 1989	XX	50	49.5	X	RCT	up TTR by 17%
Ansell 1995	XX	40	45.8	X X	Cohort	up TTR by 20%
Horskotte 1996	X	150		X X	RCT	up TTR by 34%
Hasenkam 1997	X	41	19-70	X X	Case control	up TTR by 24%
Beyth 1997	XXX	325	75	X X	RCT	up TTR by 24%
Sawicki 1999	XX	179	55	X X	RCT	up TTR by 23%
GELIA	X	278		X X	RCT	up TTR by 11%

ESCAT	X	1200		X X	RCT	up TTR by 18%
Cromheecke 2000	XXX	50	42	X X	RCT	up TTR by 6%
Watzke 2000	XXX	102	53	X X	RCT	up TTR by 11%

PST = patient self testing
PSM = patient self-management

Is the use of home INR monitor for testing PT at least equivalent to lab testing/physician office testing with respect to time in therapeutic range (TTR)?

Since the original committee recommendation in 1997, there have been several more articles published relating to the use of this device, both in terms of patient self-testing, and self-management. This primarily new body of literature demonstrates that the use of the home INR monitor is at least equivalent to lab/testing or physician office testing with respect to TTR. The studies are consistent in demonstrating that the use of the home INR monitor significantly increases TTR. There was no study that showed these home devices resulted in decreased, or equivalent TTR. The studies, which were conducted by different investigators at different sites, with different patient populations, and spread over a decade, were all consistent. We are unaware of conflicting data on this topic.

It needs to be noted, however, that although the studies were fairly well-done, there are some concerns. For example, some studies were relatively short in duration. White studied patients for 8 weeks while Ansell followed patients for almost four years; the majority of studies followed patients for approximately a year. Longer studies did not show any significant variation in terms of results; that is, the effect was not blunted.

In addition, there could be potential for selection bias. For instance, Ansell, Hasenkam, Watzke selected patients based on the stability of the PT as well as demonstrated compliance. At the same time, however, Sawicki and White chose patients who had poor control at baseline. These different selection criteria most likely had little effect, since the results were consistent across studies. A source of selection bias could be those persons capable of undergoing a self-management and self-training education session, but that is the population upon which the decision focuses.

In toto, the evidence suggests that the benefits of home INR testing/monitoring are most likely more than a result of simply increased frequency of PT INR testing that is made feasible by the use of these devices in the home. Reasons that the use of these devices can lead to increased TTR include:

- More information allows the patient to make adjustments more quickly.
- More frequent testing also provides the ability to detect any drift in INR stability sooner, rather than later, thus keeping INR within a set range.
- Greater TTR is also probably a result of the fact that PST allows the patient to evaluate how lifestyle events affect INR stability. This timely feedback may then allow the patient to modify lifestyle elements and thereby improve INR stability.
- Frequent INR results may increase physician comfort with targeting INR in the therapeutic range rather than underanticoagulating as a strategy for minimizing dangerously high INR occurring during the usual 4 to 6 week interval between tests.

Testing at home allows not only for an increased frequency of testing, but also improved timeliness, providing the ability to perform the test when it is needed. In addition, the data showed less fluctuation in values.

Now, there could be concern that a testing frequency bias exists, i.e. by simply testing more often, values will be more likely to have less variation. The patients using home monitors tested much more often, as a group, than those patients going to physician offices, or anticoagulation clinics. It is true that an average of a small number of values is more likely to be extreme than the average of a large number of values. So the probability that an individual's average INR will be out of range decreases as the number of tests increases. Therefore, the proportion of patients with average INRs out of range may decrease as number of tests increases. However, it is important to note that the metric of percentage of tests out of range or patient-days out of range (i.e. TTR) is not similarly biased by number of tests. All things being equal, increased frequency of testing should lead to a more accurate assessment of TTR. Whether this will increase or decrease TTR would seem to depend on circumstances, without any large nor consistent bias observed. Almost all studies reported data in several statistical frameworks.

In addition, one might infer from these studies that simply testing more often, irrespective of the use of a home monitor, will result in increased TTR, and perhaps decreased thromboembolic/hemorrhagic events. Such an inference would not be justified by the data for several reasons. First, the difference between the use of the device and testing in a physician office or anticoagulation clinic is more than simply increased testing. The use of these devices includes a constellation of services, including self-testing, self-management, self-empowerment, increased education, greater awareness, etc. One cannot ascribe any benefits simply to the fact that patients tested more often with a home device. Second, there are several studies with similar testing intervals (e.g. Ansell, Cromheecke) that demonstrated a difference in TTR. If testing frequency accounted completely for improved results, there should have been no differences between these groups. Third, Cromheecke performed a cross-over study. The self-testing group demonstrated a greater % of time in the therapeutic range. Therefore, simply allowing/encouraging increased testing would not guarantee improved results.

Is the use of home INR monitor for testing PT at least equivalent to lab testing/physician office testing with respect to incidence of thromboembolic events and/or hemorrhagic events?

Thromboembolic events and hemorrhagic events have a very small incidence; for patients with mechanical valves, it is 8% per year; for patients with atrial fibrillation, it is 4.5% (range 3-10%) per year. With proper anticoagulation, the rate decreases to 2%; for atrial fibrillation, it decreases to 1.5%. [13]

In small randomized clinical trials, it would be difficult to demonstrate difference in events that occur infrequently. Most of the studies reviewed showed no difference, or a small reduction in adverse events, although they were generally not statistically significant. However, one must examine negative studies very closely. These studies could have been underpowered to detect a difference; that is, there could actually be a difference but the study did not enroll enough patients to detect a difference.

Two studies did demonstrate a statistically significant difference in event rates; these studies were ESCAT and Beyth. ESCAT showed a 40% reduction in events requiring hospitalization, while Beyth showed a greater than 50% reduction in hemorrhage.

Of note, if the use of these home devices reduces the frequency of adverse events or simply facilitate a treatment, it may lead to an increase in the appropriate prescribing of oral anticoagulants by physicians who previously were reluctant to use these agents.

Given that the incidence of thromboembolic and/or hemorrhagic events are small, and some studies may be underpowered to detect a difference in incidence amongst various management methods, is TTR an adequate surrogate for reduction in thromboembolic/hemorrhagic events?

Although there were two studies that showed a decrease in the incidence of thromboembolic and hemorrhagic events, it is still worthwhile to discuss the role of surrogate measures. Surrogate measures often come into consideration when the primary measure has a small incidence. As noted earlier in the text, the incidence of the thromboembolic and hemorrhagic events is very small; in such a setting, a study would need to enroll hundreds to thousands of patients in order to have enough power to detect a statistically significant difference in events. (This explains why it is only the very large studies that are showing such differences). Such a sample size is not always plausible, so surrogate measures are often used. 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. [14] (See Appendix B for a reference list of the key articles). The authors conclude that "there is a strong relationship between TTR and event rate that is supported by a large literature."

Who is the appropriate patient population?

As noted at the beginning of this document, there are numerous indications for anticoagulation, some more generally accepted than others. It is universally agreed that all patients with mechanical heart valves need to be anticoagulated. The implications of chronic anticoagulation are often critical to the decision to place a mechanical valve in a patient. Other indications do not have universal agreement, although most people would agree that patients with atrial fibrillation, and evidence of a thrombotic stroke, would benefit from anticoagulation. In addition, patients with mechanical heart valves are anticoagulated at higher levels than patients anticoagulated for other indications, which puts them at greater risk of adverse events from the warfarin. Because these patients are unavoidably at high risk, it is important to provide the means for minimizing the risk.

Most of the studies also dealt with patients being chronically anticoagulated. Although there were a few studies dealing with short-term anticoagulation, they were not as well-designed, and the benefit of this device for such patients has not yet been demonstrated.

The evidence for a benefit for home INR monitoring is clearest for patients with mechanical heart valves. Review of the studies demonstrate that most patients enrolled in the studies were patients with mechanical heart valves. Although there were numerous indications, 90% of the patients in the studies reviewed were using the monitor for a mechanical heart valve.

The data for patients with mechanical heart valves may not necessarily be generalized to patients with other indications for anticoagulation for the following reasons:

- All patients with mechanical heart valves need to be anticoagulated, whereas some patients with atrial fibrillation may not be anticoagulated (e.g. young, non-valve AF). This select group of patients would likely be especially receptive to the use of home INR monitors, and thus achieve the greatest benefit.
- Patients with mechanical heart valves need to be anticoagulated for life, whereas the other indications do not necessarily require lifelong anticoagulation
- Patients with mechanical heart valves need to be anticoagulated at a higher range, with a greater potential risk of complications. Thus, the magnitude of benefit is greatest for this indication.
- Patients with mechanical heart valves have a greater incidence of thrombus formation, and this thrombus may be slightly different than thrombi developed in other conditions.

Based on these reasons, we are announcing our intention to issue a national coverage decision relating to the home PT (NR) monitoring for patients with mechanical heart valves. The data on the other indications is suggestive, and we look forward to receiving more information, particularly for patients with atrial fibrillation and other high risk patients such as individuals who have had a cerebrovascular accident or transient ischemic attack. We would like to see additional data on the use of these devices on other indications for anticoagulation before we consider expanding coverage.

Of note, the Veterans Administration will be embarking on a large trial relating to the use of home INR monitors, The Home INR Study (THINRS). The study, a multicenter, multiyear trial (3 years - 1 year recruitment, 2 years follow-up) addresses a slightly different set of questions than those considered in this decision. The VA study is intended to address:

- What patient populations benefit most from home INR testing, especially as it relates to the VA population, which is often different than the Medicare population?
- What is the optimal frequency of testing?
- What are the resource implications of home INR testing?

It will compare outcomes between patient self-testing with a home monitor versus an anticoagulation service. The VA study is not intended to provide data to specifically address the safety and efficacy of home prothrombin monitors in patients with mechanical heart valves.

As to the need for self-testing and self management, the more rigorous studies had patients self-test and self-manage with a physician-prescribed algorithm. All patients in the studies who self-managed underwent some type of education sessions on anticoagulation and the use of the home INR monitors. We would expect to see such educational sessions before a patient starts doing home monitoring. Every patient with a mechanical heart valve may not be a good candidate for using these devices. The use of these devices requires some manual dexterity and an ability to follow instructions. Patients should also undergo an educational program.

This program should be directed toward understanding the reason for anticoagulation, the risks of INR values above and below the therapeutic range, the time course of activity for anticoagulant drugs and the interaction with other drugs, use of the home INR device, and what action needs to be taken depending on the test result. The patient should also have demonstrated ability to follow a physician-derived algorithm relating to dosing changes.

With regards to frequency, testing will be covered at a maximum of once a week. As Table 10 demonstrates, in order to achieve time in therapeutic range of > 90%, a patient most likely needs to be tested once a week.

Table 10: TTR by Frequency of Testing

Study	*TTR*	*Frequency*
Gottlieb 1994	50%	25 days

Horstkotte 1998	59%	19 days
Cannegeiter 1995	61%	18.9 days
Ansell 1995	66%	16 days
Palaretti 1996	68%	15 days
Ansell 1995	89%	13.8 days
Horstkotte 1998	92%	4 days

Given that the half-life of warfarin is approximately 1.5 days, and it typically requires 3-4 half-lives to reach steady state, it would generally not be necessary to test more than once a week. Therefore, initial frequency parameters will be once a week testing.

Conclusion

The studies reviewed demonstrated that home prothrombin monitoring significantly improve time in therapeutic range for select groups of patients, compared to testing done in physician offices, or anticoagulation clinics. Increased TTR leads to improved clinical outcomes, with reductions in thromboembolic and hemorrhagic events. The body of evidence is suggestive, but notable weaknesses, as described earlier, still exist.

At this point in time, we are announcing our intention to issue a national coverage decision covering home prothrombin monitoring with the use of these devices for patients with mechanical heart valves, since these patients have a unique need, and they were the patients primarily studied. It is unclear if other patient populations are as likely to benefit. In addition, patients should have been anticoagulated for at least three months prior to use of the device and should undergo an educational program on anticoagulation management and the use of this device. Self-testing with the use of the devices should not occur more frequently than once a week.

Consistent with the mandates of section 4554 (b) (1) of the Balance Budget Act, the NCD for INR monitoring cannot be effective until after the Secretary has first adopted national coverage and administrative policies for clinical diagnostic laboratory tests. Thus, the agency will issue a national coverage decision covering INR monitoring once the Secretary has adopted such policies.

We are interested in reviewing data on other indications as it becomes available. We welcome interested parties to come to CMS to discuss appropriate study design and outcome measures.

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1 Hirsh JH, et al. Oral anticoagulants: mechanism of action, clinical effectiveness, and optimal therapeutic range. *Chest* 2001;119:8S-21S.

2 Laupacis A, et al. Antithrombotic therapy in atrial fibrillation. *Chest* 1998;114:579S-589S.

3 Wolf P, Abbott R, Kannell W. Atrial fibrillation as an independent risk factor for stroke: the Framingham study. *Stroke* 1991;22:983-988.

4 McCrory DC, Matchar DB, Samsa G, Sanders LL, Prtichett EL. Physician attitudes about anticoagulation for nonvalvular atrial fibrillation in the elderly. *Archives of Internal Medicine* 1995;155:277-281.

5 Antani MR, Beyth RJ, et al. Failure to prescribe warfarin to patients with nonrheumatic atrial fibrillation. *Journal of General Internal Medicine* 1996;11:721-728.

6 Common interacting drugs include several antibiotics, heart medications, antihyperlipidemic agents, and some NSAIDS - drugs that are quite frequently used in the elderly population.

7 Therapeutic index relates the dose of a drug required to produce a desired effect to that which produces an undesired effect (median toxic dose/median effective dose). Narrow therapeutic index drugs are those that have less than a two-fold difference between median lethal dose and median effective dose.

8 These clinics are sometimes referred to as Coumadin ® clinic

9 Waived tests was a category created so that physician's offices could perform tests at low risk, and without requiring all the personnel, proficiency testing, and quality assurance standards; they do require quality control. 42 CFR 493.15

10 This information is presented for historical reference. Committee information was not used as part of this national coverage decision.

11 Section 1862 (a) (1) (A) of the Social Security Act

12 Grade I: complaint mentioned, but no consequence;Grade II: complaint led to a practitioner or outpatient visit sought;Grade III: complaint led to hospital admission;Grade IV: complaint led to death

13 Atrial Fibrillation Investigators. Risk factors for stroke and efficacy of antithrombotic therapy in atrial fibrillation: analysis of pooled data from 5 randomized clinical trials. *Archives of Internal Medicine* 1994;154:1449-1457.

14 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.

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