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

Decision Summary

Our National Coverage Determination (NCD) is at § 190.11 of the Medicare NCD manual. After examining additional medical evidence, we are expanding Medicare coverage of home prothrombin (INR) monitoring to include chronic atrial fibrillation and venous thromboembolism under the following conditions:

- The beneficiary requires chronic oral anticoagulation with warfarin for a mechanical heart valve, chronic atrial fibrillation, or venous thromboembolism; and
- the beneficiary has been anticoagulated for at least three months prior to use of the home INR device; and
- the beneficiary has undergone a face-to-face educational program on anticoagulation management and demonstrated the correct use of the device prior to its use in the home; and
- the beneficiary continues to correctly use the device in the context of the management of the anticoagulation therapy following initiation of home monitoring; and
- home-testing with the device occurs no more frequently than once a week

This NCD is distinct from and makes no changes to the Prothrombin Time clinical laboratory NCD at 190.17 of the National Coverage Determinations Manual.

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Decision Memo

TO: Administrative File: CAG #00087R
Prothrombin Time (INR) Monitor for Home Anticoagulation Management

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SUBJECT: Decision Memorandum for Prothrombin Time (INR) Monitor for Home Anticoagulation Management

DATE: March 19, 2008

I. Decision

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II. Background

For consistency, unless citing the work of others, we will use the terms “PT”, “INR” and/or “PT/INR” in this memorandum to refer to the measurement of anticoagulation with the prothrombin time and/or the international normalized ratio. We recognize that alternative nomenclature may be used. Unless citing the work of others, we use the term "TTR" in this memorandum to refer to time in therapeutic target range. This is defined as the number of patient-days of follow-up which were within target range divided by the total number of patient -days included in the follow-up period (Samsa and Matchar 1999). The scope of this memorandum is not limited by the use of alternative nomenclature.

In addition, based on public input we will use the term “venous thromboembolism” to include deep venous thrombosis and pulmonary embolism.

Oral anticoagulation therapy
Warfarin is a self-administered oral anticoagulant medication and is not a Medicare Part B benefit. However, we are including a brief discussion here for the benefit of the lay reader. Warfarin, sometimes referred to under the trade name Coumadin®, is actually marketed by several manufacturers under a variety of trade names. Warfarin affects the vitamin K-dependent clotting factors II, VII, IX and X.

Coagulation

There are two biological pathways of coagulation (intrinsic and extrinsic) that converge in a common coagulation pathway. 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) test assesses the intrinsic pathway while the prothrombin time (PT) test assesses 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 indications 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 to the mean PT for a group of normal individuals is calculated. The ratio is adjusted for the sensitivity of the laboratory's thromboplastin as 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

The duration of anticoagulation therapy varies with the underlying indication and with the patient’s response to therapy. Some conditions require anticoagulation for only a period of a few months, while other conditions require long-term and possibly life-long anticoagulation. Home management is historically focused on patients needing long-term or life-long coagulation.

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. Despite numerous guidelines recommending anticoagulation for several indications, thousands of patients are not adequately anticoagulated. This underutilization disproportionately affects Medicare beneficiaries since most patients needing anticoagulation are in the Medicare aged population. Several studies suggest that the percentage of patients in non-therapeutic range (over- or under-anticoagulated), may be as high as 58-77% (Sawick 1999, Newman 2006). Some patients may have an indication for anticoagulation but are not on anticoagulants due to perceived contraindications, physician misgivings about the patient's ability to safely comply with treatment, misinformation, or other concerns. Given the narrow therapeutic index of warfarin, many physicians are fearful of anticoagulation and may be reluctant to place patients, especially elderly patients, on an anticoagulation regimen.

Managing Anticoagulation
There are at least three strategies for managing warfarin anticoagulation:

- Physician office-based testing and management
- Anticoagulation clinics
- Home PT/INR monitoring with patient reporting or physician-directed self management.

Most patients being anticoagulated are managed through physician offices, the "usual care" approach. Individual physicians manage their patients and PT/INR test frequency is generally once every 4-6 weeks. Approximately 20% of patients receive their care through an anticoagulation service, comprised of nurses, physicians and a pharmacist. 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.

Frequency of Testing
In general, most patients who are stable on chronic warfarin therapy are tested approximately once a month. The general recommendation that warfarin monitoring should be performed once every 4-6 weeks, recognizes a practical balance between the burden of frequent testing and the risk of adverse events. However, some feel this frequency is inadequate for many patients.

There are numerous factors that affect the biologic action of warfarin in an individual patient, such as inconsistent dietary vitamin K intake, the use of other drugs that interact with warfarin or affect its metabolism, and variable binding to plasma proteins. As a result, treatment of each patient can be highly individualized and may lead to frequent testing, particularly when warfarin therapy is begun or when changes are made in the patient's use of other drugs. As noted earlier, warfarin has a narrow therapeutic index. 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.

Oral anticoagulant therapy has a minor bleeding complication rate of 10-20% and major bleeding episodes occur in 1-5% of cases. Too much warfarin can have serious effects as previously discussed. Numerous studies in the literature demonstrate that an INR > 3 results in higher risk of serious hemorrhage. An INR of 4 nearly doubles the risk. Of comparable concern is subtherapeutic anticoagulation. Inadequate dosage can also lead to serious consequences. Numerous studies demonstrate that INR below 2.0 results in a higher risk of strokes. This risk increases rapidly as INR drops below this threshold.

III. History of Medicare Coverage

Medicare's national coverage determination (NCD), effective July 1, 2002, currently available at 190.11 of the National Coverage Determinations Manual, limits coverage of home PT/INR monitoring to anticoagulation management for patients with mechanical heart valves who are on warfarin. The monitor and the home testing must be prescribed by a treating physician as required by 42 CFR 410.32(a) and the following requirements must be met:

1. The patient must have been anticoagulated for at least three months prior to use of the home INR device; and

2. The patient must undergo an educational program on anticoagulation management and the use of the device prior to its use in the home; and

3. Self-testing with the device should not occur more frequently than once a week.

Current Request

CMS received a formal complete written request for reconsideration from the Prothrombin-Time Self Testing Coalition via its counsel McDermott Will & Emery LLP, signed by Larry Cohen of International Technidyne Corporation, David Phillips of HemoSense, Inc. and John Ridge of Roche Diagnostics Corporation. The requestor asked CMS to expand the population eligible for coverage of home PT/INR monitoring to patients on warfarin, as the black box warning on the label for warfarin states that “Regular monitoring of INR should be performed on all treated patients.” The requestor has asked for the addition of atrial fibrillation and deep vein thrombosis as covered indications as an alternative. The requestor also asked that we leave intact the three requirements in the current NCD.

Benefit Category

Medicare is a defined benefit program. For an item or service to be covered by the Medicare program, it must fall within one or more of the statutorily defined benefit categories outlined in the Social Security Act (the Act). § 1812 (scope of Part A); § 1832 (scope of Part B); § 1861(s) definition of medical and other services). The information provided supports continuing the current benefit category of the Act section 1861(s)(3), “diagnostic laboratory tests and other diagnostic tests,” for the new indication.

This may not be an exhaustive list of all applicable Medicare benefit categories for this item or service.

IV. Timeline of Recent Activities

June 26, 2007:	CMS posted a tracking sheet on the website and the initial 30 day public comment period began.
December 20, 2007:	CMS posted a proposed decision with a 30 day public comment period.
January 19, 2008:	CMS public comment period on proposed draft ended.

V. FDA Status

FDA has cleared 6 tests for prescriptive home use for prothrombin assays, only three are active at this point.

1. International Technidyne Corporation - ProTime Microcoagulation System, k010599
2. HemoSense - INRatio, k021923
3. Roche Diagnostic Corporation - CoaguChek XS and CoaguChek PST, k062925, k962571
4. LifeScan Inc.-Rubicon Prothrombin Time Monitoring System, k001699, k022922 ** No Active Listing
5. Avocet Medical, Inc. - Avocet AccuSure System, k991286 **No Active Listing
6. Boehringer Mannheim Corporation, K962571 **bought out by Roche Diagnostic

Manufacturer	Name of Device	K Number	Study done for approval
Roche Diagnostic	CoaguChek PST	k962571	

Manufacturer	Name of Device	K Number	Study done for approval
			317 samples compared trained patients to healthcare professionals
Roche Diagnostic	CoaguChek XS	k062925	258 samples compared trained patients to healthcare professionals
International Technidyne	ProTime Microcoagulation	k961835 k010599 (modification)	84 samples (tested multiple times)compared trained patients to healthcare professionals
HemoSense	INRatio	k021923	246 compared trained patients to healthcare professionals
LifeScan	Rubicon Prothrombin	k001699	217 Samples compared trained patients to healthcare professionals
LifeScan	Rubicon Prothrombin	k022922 (modification)	

Manufacturer	Name of Device	K Number	Study done for approval
Avocet Medical	Avocet AccuSure	k991286	389 samples compared trained patients to healthcare professionals
Boehringer Mannheim	CoaguChek PST	k962571 (Same as Roche)	

Since October 4, 2006, the FDA approved labeling for Coumadin® has included the following Black Boxed 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**).

VI. General Methodological Principles

When making national coverage determinations, CMS evaluates relevant clinical evidence to determine whether or not the evidence is of sufficient quality to support a finding that an item or service falling within a benefit category is reasonable and necessary for the diagnosis or treatment of illness or injury or to improve the functioning of a malformed body member. The critical appraisal of the evidence enables us to determine to what degree we are confident that: 1) the specific assessment questions can be answered conclusively; and 2) the intervention will improve health outcomes for patients. An improved health outcome is one of several considerations in determining whether an item or service is reasonable and necessary.

A detailed account of the methodological principles of study design that are used to assess the relevant literature on a therapeutic or diagnostic item or service for specific conditions can be found in Appendix A. In general, features of clinical studies that improve quality and decrease bias include the selection of a clinically relevant cohort, the consistent use of a single good reference standard and the blinding of readers of the index test and reference test results.

Public comment sometimes cites the published clinical evidence and gives CMS useful information. Public comments that give information on unpublished evidence such as the results of individual practitioners or patients are less rigorous and therefore less useful for making a coverage determination.

VII. Evidence

A. Introduction

We are providing a summary of the evidence that we considered during our review.

B. Discussion of evidence reviewed

1. Questions

1. *Is the evidence sufficient to conclude that anticoagulation therapy management using home PT/INR monitoring produces a clinically meaningful reduction in the incidence of thromboembolic and/or hemorrhagic events in patients treated with long-term oral anticoagulation who do not have mechanical heart valves?*

2. *If the answers to Question 1 and 2 are affirmative, what characteristics of the patient, the disease, or the treatment regimen reliably predict a favorable or unfavorable health outcome?*

Outcomes

CMS is particularly interested in evidence regarding clinically meaningful health outcomes experienced by Medicare beneficiaries. For example, we would assign more weight to evidence regarding mortality and serious adverse events such as strokes and hemorrhage than to evidence of changes in a test result that do not result in changes in the physician's management of the patient's condition.

Samsa and Matchar (1999) defined the two intermediate outcomes most used in the anticoagulation literature.

The proportion of INR values within target range is defined as the number of INRs within target range divided by the number of PT tests. The resulting figure is simple to calculate but biased…the figure is affected by the tendency for physicians to perform repeated tests soon after an out-of-range INR. It can be demonstrated that this bias increases as the interval between tests increases.

The time in target range involves first linearly interpolating between observed test values in order to extrapolate data points on a daily basis, then defining TTR as the number of patient-days of follow-up which were within target range divided by the total number of patient-days included in the follow-up period. A deficiency of TTR is that it depends on the choice of INR range. TTR contains more information than proportion of INR values within target range. It is the preferred measure.

2. External technology assessments

We did not request an external technology assessment (TA) on this issue and are unaware of any assessments that have been conducted independently.

3. Internal technology assessments

Literature Search

CMS performed an extensive literature search utilizing PubMed for randomized controlled trials (RCTs) and systematic reviews evaluating the use of prothrombin time INR monitoring for home anticoagulation management The literature search was limited to the English language, publication dates from January 2001 through August 2007 and specific to the human population. Search terms were: anticoag* or warfarin or coumadin or coumarin* AND INR or prothrombin or PT or international normal*ratio AND self. CMS also reviewed any literature submitted by the requestor or in public comments.

Evidence Reviewed

CMS extensively reviewed the body of literature on the use of home monitoring in the decision memorandum released in 2001. (See http://www.cms.hhs.gov/mcd/viewdecisionmemo.asp?id=72#P119_5825#P119_5825). We will not present that evidence again in this reconsideration decision.

The 2001 NCD for home PT/INR monitoring restricted Medicare coverage of home testing to patients with mechanical heart valves since the majority of the medical literature addressed only this subset of patients. Since that time, there have been several articles published on both patient self testing (PST) and patient self management (PSM) in various patient populations. Additionally, both the American Heart Association and American College of Cardiology have released position statements supporting the use of home monitors for the management of specific patients needing long-term anticoagulation (Hirsh 2003).

The literature base has expanded since 2001 to include several articles on self-management of PT/INR as well as patient self testing (Table 1). Though this NCD is addressing only the ability of patients to self-test for their anticoagulation status, much of the literature evaluated is related to self-management, where the patient, in concert with a physician consultation and subsequent education, adjust their anticoagulation therapy based on a predetermined dosing schedule. All study patients received some sort of face-to-face training.
Below is a brief summary of the articles used in this decision memorandum.

TABLE 1: Brief Summary of Current Studies

AUTHOR YEAR	INDICATIONS				N	MEAN AGE	PST	PSM	STUDY TYPE
	MHV	AF	DVT	OTHER					
Gardiner 2004	X	X	X	X	84	59	X		RCT
Gardiner 2005	X	X	X	X	104	59-60.9	X		RCT
OAMSG 2001	X	X	X	X	82	55	X		Prospective cohort
Menendez-Jandula, 2005	X	X	X		737	64-67		X	RCT
Sunderji 2004	X	X	X	X	140	57.6-62.3		X	RCT
Fitzmaurice2002	?	X	?	?	56	63-69		X	

									RCT
Fitzmaurice2005	X	X	X	X	617	65		X	RCT
Heidinger 2000		X	X		1375	50-57		X	Retrospective case series
Völler (SMAAF) 2005		X			202	64.3		X	RCT
Voeller 2005	X	X	X	X	330	54-68		X	RCT

PST = patient self testing
PSM = patient self-management
MHV = mechanical heart valve
AF = atrial fibrillation
DVT = deep vein (or venous) thrombosis

Summary of the evidence by study type

1. Patient self–testing studies

Gardiner, et al. (2002)

The investigators randomized 84 patients who had received long-term oral anticoagulation for at least 8 months to either patient self-testing or the control group. Patients in the self-testing group had face-to-face training and then tested themselves at home once a week and recorded the result for a 6-month period. Laboratory INR tests were performed every 4 weeks. For the self-testing group a comparison was done between the laboratory INR test and a self-test. Outcomes analyzed were mean INR values and observed time in therapeutic range (TTR).

The primary indications for anticoagulation were:

- Atrial fibrillation (n=23)
- Replacement heart valve (n=25)
- Venous thromboembolism (n=24)
- Cardiovascular prophylaxis (n=8)
- Cerebrovascular prophylaxis (n=4)

No significant differences were found between self-testing and laboratory INRs. No significant difference in TTR was seen between the two groups. Each study group had five minor bleeding or bruising events. A majority (87%) of patients found self-testing straightforward and 77% preferred it over going to the clinic. The authors conclude that patient self-monitoring offers a reliable alternative to laboratory determination of INR and is acceptable to the majority of suitably trained patients.

Of the patients eligible, there was a low enrollment (10%). This suggests that only a minority of patients may be motivated enough to participate in these programs and limits the generalizability of the results.

Gardiner, et al. (2005)

In a more recent study, 104 patients were randomized to self-testing or self-management. The subjects were receiving long-term anticoagulation treatment for a period of at least 8 months. Both groups attended a face-to-face training session with a nurse practitioner. Subjects in the patient self-monitoring group then tested their INR every 2 weeks for a period of 6 months and made dosing changes based on a treatment algorithm issued to them. Patients in the self-testing group also tested once every 2 weeks for 6 months. They contacted the anticoagulation clinic staff with the INR result so they might be advised of dosing changes.

The primary indications for anticoagulation were:

- Atrial fibrillation (n=42)
- Replacement heart valve (n=24)
- Venous thromboembolic (n=20)
- Cardiovascular prophylaxis (n= 8)
- Cerebrovascular prophylaxis (n=10)

Overall, no statistically significant difference in the TTR was found between the two groups (self management =69.9% and self-testing was 71.8%). When compared to the patient's historical data, no statistically significant differences were found between the TTR in the prior 6 months as compared to the results from self-monitoring/testing. The percentage of time spent outside the desired range in the self-testing group was approximately half of that observed in the previous 6 months. Only a modest improvement was seen in the self-managing patients. Both the patient self testing and patient self-management groups spent more time in the target range while in the study. The authors concluded that patient self-monitoring is an effective mode of oral anticoagulant management for the majority of suitably trained patients.

Limitations include low participation (13%) and a lack of blinding. Both present a potential bias towards the preferred outcome (self-management).

<u>The Oral Anticoagulation Monitoring Study Group (OAMSG) (2001)</u>

This was a prospective cohort study (n=82) evaluating the accuracy and reliability of the device in trained patient self-testing candidates. All patients received face-to-face training on the use of the home anticoagulation monitor and then were evaluated on their ability to use the home monitor.

The study was a split-sample design where the patients served as their own controls. Outcomes of interest included a comparison of the PT results at home with those obtained for the same test period by the clinic and the reference laboratory. The percentage of test results that fell within, above, or below the therapeutic range for each patient was quantified for each type of measurement. At the end of the study, patients were asked to complete a questionnaire that assessed their ability to perform the self-testing.

Primary indications for anticoagulation were:

- Heart valve replacement (n=20)
- Prophylaxis for deep venous thrombosis (n=15)
- Atrial fibrillation (n=14)
- Stroke/cerebrovascular accident (n=10)
- Treatment of acute deep venous thrombosis (n=9)
- Pulmonary embolism (n=5)
- Myocardial infarction (n=3)
- Other (n=6)

There was a high degree of similarity (r=0.92) between the home and clinic results. There was also good agreement (r=0.86) between the home test result and the reference laboratory result. Using the reference laboratory as a standard, 68% of the hospital results and 66% of the home results matched the therapeutic range of the reference result. When a mismatch occurred, the home or clinic result was more likely to be low compared with the reference laboratory result.

Patients overwhelmingly reported satisfaction with the ease of the use of the device and preferred the home monitoring over the venous blood collection at the clinic. The home monitor yielded accurate and precise results in the hands of patients in the nonprofessional setting.

The authors concluded that properly selected and suitably trained patients are capable of routinely performing home anticoagulation measurements with a point-of-care device.

2. Patient self management studies

Menéndez-Jándula, et al. (2005)
The investigators randomized 737 ambulatory patients receiving long-term anticoagulant therapy for at least 3 months to patient self-management and conventional management and then stratified according to sex and age (≥70 years of age or <70 years of age). The conventional management group had INR checks every 4 weeks at the hospital. If the result was out of the target range the next appointment was set for 1 or 2 weeks based on the dosing protocol. The self-management group received face-to-face training and a nurse evaluated the patient's expertise in self-management. The self-management group then performed the INR test at home once per week and determined the appropriate dose and the time of the next INR test.

Outcomes analyzed included percentage of INR values within target range, TTR and thromboembolic or hemorrhagic events. Nine of the 369 withdrew after randomization. Fifty-eight of the 368 patients declined to participate because they lacked confidence. Ten patients (mean age 70 years old) could not pass the course for self-management and returned to conventional management. They were included in the intention to treat (ITT) analysis as self-management patients.

In the control arm, 27 patients had major complications and 134 reported minor hemorrhagic events. Fifteen control patients died during the study. Eight patients in the self management group had major complications and 55 reported minor hemorrhages. Six self-managed patients died.

Primary indications for anticoagulation were:

- Atrial fibrillation, dilated cardiomyopathy, valve disease, biological prosthesis (n=371)
- Mechanical aortic prosthesis (n=125)
- Mechanical mitral, tricuspid, or multiple prosthesis (n=149)
- Venous thrombophilia (n=92)

The TTR was not statistically different between the groups. There was no relationship between the percentage of INR tests within target range or the time within target range and age, educational level, or indication for oral anticoagulant treatment. The authors concluded that patient self-management of oral anticoagulation treatment is similar to management by a specialized clinic when measured by the quality of INR control.

Sunderji R, et al. (2004)
The investigators randomized 140 patients who were on warfarin for at least one month and their clinical condition required an INR value either within 2.0-3.0 or 2.5-3.5. Patients assigned to the self-management group had extensive face-to-face training and tested their INR using a point-of-care device and adjusted their warfarin doses using a nomogram. Outcomes of interest were a 20% improvement in anticoagulation control by self-management compared to physician-management (assessed by proportion of INR measurements that were within the target range and the time in the target range), mean interval between INR measurement and complication rates.

Primary indications for anticoagulation were:

- Mechanical valve (n=82)

- Atrial fibrillation (n=47)
- Venous thromboembolism (n=7)
- Other (n=3)

The observed difference in anticoagulation control was not significantly different between the two groups for either INR results within target range or time in target range. There were three major adverse events in the control arm. All patients that completed the self-management arm indicated that they were satisfied with using the point-of-care monitor for INR testing and adjustment of their own warfarin dose.

There were several limitations. The unanticipated early dropout of 13 patients from the self-management arm (before starting self-management) reduced the power to detect a significant difference in the complication rates between the groups. Another limitation is the open-label design. Bias may have been introduced with the monthly contact between pharmacist and patient only for those patients in the self-management arm. Additionally, only the self management group received education about warfarin and it is unclear if this might have biased the results. It remains unclear if similar improvement would have been seen in the control arm if they had been educated similarly.

Regardless, the authors conclude that the results support self-management as a feasible model of anticoagulation management.

Fitzmaurice, et al. (2002)
The investigators randomized patients (n=56) attending clinic receiving long term anticoagulation treatment for a period of at least 6 months, with satisfactory INR control to either patient self-management or routine clinic management. Most had atrial fibrillation (the percentage was not reported). Patients in the self-management group had extensive face-to-training and evaluation.

Outcomes of interest were: percentage of time in INR range, percentage of tests in INR range and adverse events.

There were no significant differences between the two groups in the percentage time in range or the proportion of test in range. Seven patients reported minor adverse events in the intervention group. There was one serious adverse event in the control group.

Limitations were that there was no report of the percentage of eligible participants who enrolled, it was not blinded and there is no report of the indications for anticoagulation except to say that they were mostly for atrial fibrillation.

The authors concluded that no significant differences in INR values or serious adverse events were found between the two groups, demonstrating that selected patients are capable of measuring their own INR and dosing their warfarin accordingly.

Fitzmaurice, et al. (2005)

The investigators attempted to determine the clinical effectiveness of self management compared with routine care in patients on long term oral anticoagulation. In this study, 617 patients from primary care centers in the UK with a long term (>12 months) indication for oral anticoagulation were randomized to either self-management or routine care.

Patients in the intervention group attended two face-to-face training sessions led by nurses. Intervention patients managed their own anticoagulation therapy for 12 months. The main outcomes of interest were the percentage of time spent within the therapeutic range and adverse events.

Clinical indications for anticoagulation were (in rank order):

- Atrial fibrillation (about 50%)
- Mechanical prosthetic heart valves
- Recurrent pulmonary embolism or deep vein thrombosis
- Cardiomyopathy
- Transient ischemic attack or stroke

No significant differences were found in percentage of time in the therapeutic range between the self-management and routine care (70% vs. 68%, respectively). Self managed patients with poor control before the study showed an improvement ($p<0.007$) in control that was not seen in the routine care group. Nine patients had serious adverse events in the patient self management group compared with 7 in the routine care arm; this was not statistically significant. There was a low enrollment rate (24% of those eligible) and comparison with routine care was difficult because of the different testing schedules.

The authors concluded that self management is an effective and safe model of care for patients who have been trained appropriately and may even represent the model of choice for patients who are poorly controlled in routine care.

Heidinger, et al. (2000)
This was a retrospective, questionnaire-based study that enrolled 1375 patients (753 with atrial fibrillation, 622 with deep vein thrombosis) who had been practicing self-management for at least 3 months, evaluated if the INR values were within therapeutic range and monitored adverse events. Patients received face-to-face training.

For both atrial fibrillation and deep vein thrombosis, approximately 69% of the INR values were within the therapeutic range. For patients with atrial fibrillation, 126 reported hemorrhagic complications and 25 reported thromboembolic events. For those with deep venous thrombosis, 145 patients reported hemorrhagic complications and 22 reported thromboembolic events. The authors concluded that self-management of oral anticoagulation is a reliable option and is suitable for monitoring therapy in patients with atrial fibrillation and deep vein thrombosis.

A significant limitation to this study was that it was a large, retrospective case series and as such cannot show causality.

Self-Management of oral Anticoagulation in nonvalvular Atrial Fibrillation (SMAAF), Völler, et al. (2005)

The SMAAF investigators conducted an RCT to establish how well the INR values were kept in the individual target range over a two year period of observation in a patient self-management group versus routine care study of patients with atrial fibrillation. Patients received face-to-face training. Adverse events were also evaluated.

2000 patients in whom long-term anticoagulation therapy was indicated because of permanent nonvalvular atrial fibrillation were to be included. Only 202 patients consented to participate during the enrollment period. Therefore, the study was discontinued early.

The values were in the target range significantly more frequently in the patients under self-management (67.8%) as compared to usual care (58.5%) ($p=0.0061$). The self-management group showed a significantly lower percent of INR values below target range (15.2%) compared with usual care (22.1%) ($p=0.0379$). There was a trend with regard to the number of days within the target range (178.8±126 days as compared to 155.9±118.4 days) for the intervention group.

One patient had 2 severe hemorrhages in the self management group and there was one thromboembolic event in the usual care group.

The significantly low enrollment (10%) prompted the discontinuation of the study, which is a limitation of this study. Hence, the results may only be suggestive of a trend.

The authors concluded that patients with atrial fibrillation appear to benefit from INR self-management. The results suggest that self-management may be more effective in attaining values within the desired INR target range than usual care.

Voeller, et al. (2005)

In this prospective cohort study 330 patients with long-term oral anticoagulation therapy were divided into two groups (usual care and self-management) based on suitability for self-management. Patients were selected according to the Association of Self-Monitoring of Anticoagulation (ASA). The usual care group had a 2-hour session on anticoagulation therapy and the self-management group had an additional face-to-face training session that also included practical experience. Complication rates in both arms were then assessed.

Indications for anticoagulation were (some patients are included in more than one category):

- Mechanical prosthetic heart valve (n=120)
- Aortic valve replacement (n=89)
- Mitral valve replacement (n=31)
- Double valve replacement (n=10)
- Biological valve replacement (n=19)
- Atrial fibrillation (n=83)
- Left ventricular dysfunction/thrombi (n=58)
- Generalized atherosclerosis, peripheral artery disease (n=25)
- Recurrent venous thromboembolism (n=15)

There was no significant difference in the overall complication rates between the two groups.

This study does not address TTR as a primary outcome and there were 47 cross-overs that were not analyzed by an intention-to-treat analysis.

The authors concluded that complication rates for patients with long-term oral anticoagulant did not differ significantly between usual care and self-management. Rather, the patient's BMI and the requirement of a high INR level impact the complication rate. The investigators determined that the complication rate did not vary by anticoagulation indication between self management and usual care

4. MedCAC

CMS did not convene the Medicare Evidence Development and Coverage Advisory Committee for this analysis.

5. Evidence-based guidelines

Though there are many published guidelines on the topic of anticoagulation therapy, we did not find any evidence based guidelines that specifically address home PT/INR testing.

6. Professional Society Position Statements

For space considerations we are not reiterating here the professional society positions that were included in the proposed decision. We refer the interested reader to that document.

American College of Cardiology

ACC supports CMS proposed recommendation to expand Medicare Part B coverage of home anticoagulation monitoring to warfarin patients with chronic atrial fibrillation and deep venous thrombosis beyond those patients with mechanical heart valves. However, the ACC urged that CMS should include patients on warfarin with congenital thrombophilic disorders, consider more frequency testing may be justified beyond once a week. The ACC also urged CMS to consider coverage for the physician services required to evaluate the test results and make necessary adjustments in the patient's therapy.

7. Expert Opinion

CMS did not solicit or receive any external expert opinion on this issue.

8. Public Comments

Initial Comment Period 06/20/2007-07/20/2007

CMS received a total of 134 comments during the public comment period (25 comments were duplicate comments). The comments were received from clinicians, health care non clinicians, patients and organizations. The majority of the comments are in favor of providing Medicare Part B coverage for PT/ INR home monitoring for anticoagulation management for all patients receiving warfarin. Nine comments are against PT/INR home monitoring for anticoagulation management for all patients receiving warfarin. Sixteen comments pertain to issues outside of the purview of this national coverage analyses, e.g. reimbursement issues, such as Medicare coverage of cognitive behavior services and telephone services in coagulation clinics).

Second Comment Period 12/20/2007-1/19/2008

During the second comment period, 53 timely comments were received.

The comments and CMS' responses are summarized below:

Comments on beneficiary education
Several comments suggested that CMS expand coverage with face-to-face instruction/training.

Response:
CMS is including this requirement in the final decision.

Comments fully supporting the proposed decision
Many comments favor expanding the Medicare Part B coverage for PT/INR home monitoring for anticoagulation management from beneficiaries on warfarin for mechanical heart valves to beneficiaries on warfarin for chronic atrial fibrillation and deep venous thrombosis

Response:
CMS appreciates the supportive comments.

Comments favoring limited expansion

- Several commenters suggest expanding coverage only to appropriate patients (or caregivers).
- Another comment notes that while home self testing for PT/INR is beneficial for many patients, not all patients should be allowed or encouraged to self test. In addition, geriatric population would have problems checking PT/INR by themselves at home.

Response:
CMS appreciates the supportive comments. The final decision allows coverage of home monitoring PT/INR for appropriate patients and permits consideration of the caregiver's assistance to the beneficiary.

Comments on documentation

- Coverage criteria should not include burdensome language or requirements and the warfarin managing provider should be the responsible entity to assess and document anticoagulation.
- The comment requested that CMS clarify that "deep venous thrombosis" includes all patients with venous thromboembolism and instruct local contractors that documentation in the medical record is sufficient to show ongoing proficiency with home PT/INR monitoring (following the initial required education and training).
- Another comment took exception to the new requirement that beneficiaries continue to correctly use the device following initial training. The comment stated that the Local Medicare contractor could interpret this as requiring a burdensome certification process. The commenter recommends that the final NCD include language specifying that physician documentation in medical record of the patient's continued correct use of the device is sufficient to meet this requirement.

Response

CMS agrees with these comments and we expect that the beneficiary's treating physician will assess and document the adequacy of the beneficiary's anticoagulation. We do not believe that the language is burdensome. We agree that deep venous thrombosis includes all patients with venous thromboembolism and have discussed this elsewhere in this decision memorandum. Since anticoagulation may be lifelong we believe in is realistic to consider that the beneficiary's functional status may deteriorate acutely or over a longer period of time to the point that he or she can no longer successfully perform his or her part of home monitoring. The Medicare contractors may provide guidance on documentation it expects to support a claim.

Comments requesting wider coverage than the proposed decision

- Other comments requested that coverage should be expanded more broadly to all situations where vitamin K antagonists [such as warfarin] are given long term to patients and that coverage should be independent of diagnosis and indication.
- For home PT/INR monitoring to suitable and trained patients requiring chronic warfarin therapy regardless of underlying indication for warfarin therapy
- For beneficiaries with left ventricular assist devices, ventricular dysfunction, strokes, post phlebitic syndrome, pulmonary embolism, and other conditions.
- To include Medicare beneficiaries with congenital thrombophilic disorders. They referred CMS to ACC/AHA guidelines developed by other organization for recommendations on frequency with which patients on anticoagulation therapy should be monitored.
- More frequent testing may be needed other than once a week.

Response
The current evidence does not support a broad national generalization to all indications for warfarin use or to more frequent testing. We remain concerned about the limited generalizability of these conclusions to broader populations. In particular, the ability of the investigators to enroll only a very small percentage of the eligible subjects leads us to determine that home testing should only be covered in patients who demonstrate the capability and motivation to test correctly in the context of the management of their anticoagulation. This includes the prompt communication of the test results to the physician and the adherence to the prescribed treatment regimen. We believe that any benefits attributable to home testing are negated if the testing is not integrated into a comprehensive therapeutic strategy. Local Medicare contractors have discretion to make determinations under §1862(a)(1)(A) on those indications that are not addressed by this NCD. We believe that the final decision balances the desire for broader access against the concerns that some patients will not test correctly and may thus be harmed.

Comment on site of services:
Another comment supports coverage through the beneficiary's physician office or through an anticoagulation clinic.

Response
This decision does not prohibit the provision of this service through the beneficiary's primary treating physician or an anticoagulation clinic.

Comment on pharmacist billing
Patient self testing training should be provided to beneficiaries by a physician or pharmacist. The comment requested information on billing Medicare for pharmacist services rendered through a warfarin clinic under a physician protocol performed by pharmacist.

Response
We agree that qualified personnel should provide face-to-face training to patients who will be engaging in home PT/INR testing. CMS regulations at 42 CFR 410.32(b) speak to the requirement for physician supervision for diagnostic tests billed under the Physician Fee Schedule. The Medicare program does not provide direct reimbursement to pharmacists for this service.

Comment on physician reimbursement

- Physicians that monitor and adjust coumadin need to be reimbursed for the time it takes to discuss results with patients and teach which is done at every visit.
- The comment urged CMS to consider coverage not only for PST testing itself, but also for the physician services required to evaluate results

Response
This NCD does not determine the amount of payment for services provided under the Physician Fee Schedule regulation. We believe that the available evaluation and management (E&M) and other codes provide a mechanism for the identification of physician claims related to this service.

Comments on Coding

- There are new CPT codes established in 2007 which provide means for reporting these services outside of a face-to-face E&M encounter, but Medicare does not reimburse separately for these services.
- Commenters suggested a requirement for face-to-face training in G0248 and documentation as such, allowing treating physicians to designate an alternative recipient of INR results, list ICD-9-CM codes for conditions that support medical necessity and propose that CMS change the descriptors of HCPCS II codes G0248 and G0249.

Response
NCDs do not determine the coding or the payment amount for items and services provided to beneficiaries. We will separately revise the HCPCS codes G0248 and G0249 to change the nomenclature for the codes to require face to face training. ICD-9-CM codes will not be listed in the NCD.

VIII. CMS Analysis

National coverage determinations (NCDs) are determinations by the Secretary with respect to whether or not a particular item or service is covered nationally under title XVIII of the Social Security Act, § 1869(f)(1)(B). In order to be covered by Medicare, an item or service must fall within one or more benefit categories contained within Part A or Part B and must not be otherwise excluded from coverage. Moreover, with limited exceptions, the expenses incurred for items or services must be “reasonable and necessary for the diagnosis or treatment of illness or injury or to improve the functioning of a malformed body member” (§ 1862(a)(1)(A)). This section presents the agency's evaluation of the evidence considered and conclusions reached for the assessment questions.

Warfarin preparations now have a labeled black boxed warning to remind practitioners that PT/INR must be monitored if patients are being anticoagulated with this drug. It is a drug that may lead to bleeding if therapeutic ranges are exceeded, but may also permit clotting if therapeutic targets are not met. Even though there are known complications of inadequate anticoagulation, many patients do not maintain their PT/INR values within the recommended therapeutic ranges. Several studies suggest that the percentage of patients in non-therapeutic range may be as high as 58-77% (Sawick 1999, Newman 2006). Given the harms of being outside of the therapeutic target range, we support the evidence-based use of available strategies to maintain better control of anticoagulation in these patients.

1.

Is the evidence sufficient to conclude that anticoagulation therapy management using home PT/INR monitoring produces a clinically meaningful increase in the time in therapeutic target range (TTR) in patients treated with long-term oral anticoagulation who do not have mechanical heart valves?

There is a significant body of clinical scientific literature to answer these questions. (See Table 1, evidence section). The majority of studies were fairly well-designed randomized clinical trials, with most patients self-testing and self-managing. Reported conclusions were consistent across indications for anticoagulation and the methodologic quality of the studies, though as we have noted above the low percentage of enrollment among eligible subjects limits the generalizability of the conclusions. This consistency is helpful. Though the majority of studies were for patient self management, all involved the basic tenet of self-testing even if the patient is later managing their anticoagulation in concert with a physician consultation. Hence, we were comfortable using these studies to support our conclusions.

Since the original NCD in 2001, there have been several more articles published relating to the use of this device, both in terms of patient self-testing and self-management and for a variety of anticoagulation indications. This new body of literature focuses mainly on atrial fibrillation and venous thromboembolism and demonstrates that in some populations the use of the home INR monitor is at least equivalent to laboratory testing or physician office testing with respect to TTR. The results are consistent across studies. There was no study that showed that these home devices resulted in decreased TTR. We are unaware of conflicting data on this topic. Though it remains unclear if the patients in the “trained” groups did better merely because they were trained, there does not seem to be a worse outcome with patient-self testing.

Although the studies were fairly well-done, there are some concerns. Low enrollment rates raise concerns of selection bias. For instance, many studies had only 10-20% enrollment rates from the eligible population (Gardiner 2004, 2005; Fitzmaurice 2005; Voeller 2005) and one was discontinued due to low enrollment (Völler (SMAAF) 2005). We are therefore challenged to generalize the conclusions beyond patients who have demonstrated capability and motivation for undergoing a self-management and self-training education session and for the ongoing use of the monitor over time.

We believe that the outcomes attributed to home INR testing/monitoring are not solely due to more frequent testing made feasible by the use of these devices in the home. Additional reasons that the use of these devices may lead to improved TTR include the following:

- Compared to sending the test to an outside laboratory, the immediate availability of test result information allows the treating physician to make dosage adjustments, if needed, more quickly.
- Self-testing may facilitate the patient’s recognition of the effect of lifestyle, including dietary factors, on INR stability. This timely feedback may facilitate the patient’s modification of lifestyle elements and thereby improve INR stability.
- The enhanced availability of INR results may increase the treating physician’s comfort to prescribe anticoagulant doses sufficient to maintain INR more fully within the therapeutic target range. Absent such comfort some treating physicians may dose to lower than ideal targets as a strategy to minimize the likelihood of a dangerously high INR during the usual 4 to 6 week interval between tests.

2.

Is the evidence sufficient to conclude that anticoagulation therapy management using home PT/INR monitoring produces a clinically meaningful reduction in the incidence of thromboembolic and/or hemorrhagic events in patients treated with long-term oral anticoagulation who do not have mechanical heart valves?

Thromboembolic events and hemorrhagic events are uncommon. The incidence for patients with mechanical valves is 8% per year; for patients with atrial fibrillation, 4.5% (range 3-10%) per year. With proper anticoagulation, the rate decreases to 2% for patients with mechanical heart valves; for atrial fibrillation, it decreases to 1.5% (Atrial Fibrillation Investigators 1994). Because of the concerns of adverse events, several studies have been conducted to examine the use of patient self testing and self management. The hypothesis behind these studies was if patients could have a less burdensome way to monitor their anticoagulation, they would in turn have better control or at least fare no worse than with routine care.

Two studies did demonstrate a decrease in event rates (Menéndez-Jándula 2005, Sunderji 2004) for patients with mechanical heart valves, atrial fibrillation and venous thromboembolism. However, the remaining studies (see Table 1) did not demonstrate a difference in event rates.

3.

If the answers to Question 1 and 2 are affirmative, what characteristics of the patient, the disease, or the treatment regimen reliably predict a favorable or unfavorable health outcome?

Indications:
As noted in the FDA approved labeling for warfarin, regular monitoring is encouraged for all patients on warfarin and frequent monitoring is encouraged for certain high risk patients. It is important to state here that the scope of this decision is specific to home PT/INR monitoring and does not apply to other PT/INR monitoring that may be undertaken to address the labeled recommendation.

As noted previously, there are numerous indications for anticoagulation, some more generally accepted than others. It is generally 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 would agree that patients with atrial fibrillation and evidence of a thrombotic stroke would benefit from anticoagulation (Hirsh 2003).

Previously, the evidence for a benefit for home INR monitoring was most clear for patients with mechanical heart valves. Review of the studies demonstrated that most patients enrolled in the studies were patients with mechanical heart valves. However, the current evidence includes a significant population with other indications for long term anticoagulation including atrial fibrillation and venous thromboembolism.

All of the reviewed studies looked at multiple indications for long-term anticoagulation. These included mechanical heart valves, atrial fibrillation and venous thromboembolism, among other indications. There were no reported differences in outcomes by indication. Though the 2001 NCD restricted the coverage of home testing to patients with mechanical heart valves, with new evidence available, we now see insufficient reason to restrict coverage to just mechanical heart valves. Thus, we are expanding coverage for the home PT (INR) monitoring to patients with atrial fibrillation and venous thromboembolism.

While there are other indications for long-term anticoagulation and the potential to use home monitoring for these indications, the body of evidence to support home PT/INR testing for these indications is not currently as robust as that for mechanical heart valve, atrial fibrillation and venous thromboembolism.

Patient education and training:

All studies had patients self-test and self-manage with a physician-prescribed algorithm. In addition, all patients in the studies who self-managed received face-to face education and training sessions on anticoagulation and the use of the home INR monitors. Furthermore, most were evaluated on their performance by trained professionals. All citations discuss the issues surrounding calibration of the testing device.

Face-to-face training has been shown to increase participation of patients in home testing and monitoring and experimental evidence shows that this type of in-person, face-to-face training can improve clinical outcomes (Beyth 2000). CMS believes that this is critically important and thus CMS will require that beneficiaries receive face-to-face education before they start home testing and as needed subsequently if they continue home testing. CMS believes that other non-face-to-face training methods do not support the beneficiary's demonstration of correct use of the device.

Not every patient with an indication for long term anticoagulation will be a good candidate for using these devices. The use of these devices requires some manual dexterity and an ability to follow instructions. The patient should also have demonstrated ability to follow a physician-derived algorithm relating to dosing changes. Finally, many studies have shown that only highly motivated patients should be enrolled in self-testing. This will likely be a minority of the patients potentially considered for this mode of testing.

Medicare local contractors may consider on a case-by-case basis the ability of a caregiver to assist the patient. For example the demonstrated presence of a family member who is consistently available in the beneficiary's home and willing and able to safely assist in the testing and medication administration usually required of the patient might allow the beneficiary to meet those provisions of this coverage decision.

We remain concerned about the limited generalizability of these conclusions to broader populations. In particular, the ability of the investigators to enroll only a very small percentage of the eligible subjects leads us to determine that home testing should only be covered in patients who demonstrate the capability and motivation to test correctly in the context of the management of their anticoagulation. This includes the prompt communication of the test results to the physician and the adherence to the prescribed treatment regimen. We believe that any benefits attributable to home testing are negated if the testing is not integrated into a comprehensive therapeutic strategy.

Frequency of testing:
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 not be generally necessary to test more than once a week in a patient who is beyond the initial titration period. Therefore, we see no need to change the current nationally covered frequency limitation. Some have noted that more frequent testing could be needed if a patient begins a new medication that may affect the metabolism of warfarin and thereby the INR. While we do not dispute that assertion, we point out that this NCD speaks only to testing performed in the home. If a patient's condition has been destabilized by a change in medication or other factor, the patient may benefit from more rather than less direct attention from the treating physician.

IX. Conclusion

Our current National Coverage Determination (NCD) is at § 190.11 of the Medicare NCD manual, coverage is limited to patients with mechanical heart valves. After examining additional medical evidence, we are expanding Medicare coverage of home prothrombin (INR) monitoring to include chronic atrial fibrillation and venous thromboembolism under the following conditions:

-

- The beneficiary requires chronic oral anticoagulation with warfarin for a mechanical heart valve, chronic atrial fibrillation, or venous thromboembolism; and

- the beneficiary has been anticoagulated for at least three months prior to use of the home INR device; and

- the beneficiary has undergone a face-to-face educational program on anticoagulation management and demonstrated the correct use of the device prior to its use in the home; and

- the beneficiary continues to correctly use the device in the context of the management of the anticoagulation therapy following initiation of home monitoring; and

- home-testing with the device occurs no more frequently than once a week.

This NCD is distinct from and makes no changes to the Prothrombin Time clinical laboratory NCD at 190.17 of the National Coverage Determinations Manual.

APPENDIX A

General Methodological Principles of Study Design
(Section VI of the Decision Memorandum)

When making national coverage determinations, CMS evaluates relevant clinical evidence to determine whether or not the evidence is of sufficient quality to support a finding that an item or service is reasonable and necessary. The overall objective for the critical appraisal of the evidence is to determine to what degree we are confident that: 1) the specific assessment questions can be answered conclusively; and 2) the intervention will improve health outcomes for patients.

We divide the assessment of clinical evidence into three stages: 1) the quality of the individual studies; 2) the generalizability of findings from individual studies to the Medicare population; and 3) overarching conclusions that can be drawn from the body of the evidence on the direction and magnitude of the intervention's potential risks and benefits.

The methodological principles described below represent a broad discussion of the issues we consider when reviewing clinical evidence. However, it should be noted that each coverage determination has its unique methodological aspects.

Assessing Individual Studies

Methodologists have developed criteria to determine weaknesses and strengths of clinical research. Strength of evidence generally refers to: 1) the scientific validity underlying study findings regarding causal relationships between health care interventions and health outcomes; and 2) the reduction of bias. In general, some of the methodological attributes associated with stronger evidence include those listed below:

- Use of randomization (allocation of patients to either intervention or control group) in order to minimize bias.
- Use of contemporaneous control groups (rather than historical controls) in order to ensure comparability between the intervention and control groups.
- Prospective (rather than retrospective) studies to ensure a more thorough and systematical assessment of factors related to outcomes.
- Larger sample sizes in studies to demonstrate both statistically significant as well as clinically significant outcomes that can be extrapolated to the Medicare population. Sample size should be large enough to make chance an unlikely explanation for what was found.
- Masking (blinding) to ensure patients and investigators do not know to which group patients were assigned (intervention or control). This is important especially in subjective outcomes, such as pain or quality of life, where enthusiasm and psychological factors may lead to an improved perceived outcome by either the patient or assessor.

Regardless of whether the design of a study is a randomized controlled trial, a non-randomized controlled trial, a cohort study or a case-control study, the primary criterion for methodological strength or quality is the extent to which differences between intervention and control groups can be attributed to the intervention studied. This is known as internal validity. Various types of bias can undermine internal validity. These include:

- Different characteristics between patients participating and those theoretically eligible for study but not participating (selection bias).
- Co-interventions or provision of care apart from the intervention under evaluation (performance bias).
- Differential assessment of outcome (detection bias).
- Occurrence and reporting of patients who do not complete the study (attrition bias).

In principle, rankings of research design have been based on the ability of each study design category to minimize these biases. A randomized controlled trial minimizes systematic bias (in theory) by selecting a sample of participants from a particular population and allocating them randomly to the intervention and control groups. Thus, in general, randomized controlled studies have been typically assigned the greatest strength, followed by non-randomized clinical trials and controlled observational studies. The design, conduct and analysis of trials are important factors as well. For example, a well designed and conducted observational study with a large sample size may provide stronger evidence than a poorly designed and conducted randomized controlled trial with a small sample size. The following is a representative list of study designs (some of which have alternative names) ranked from most to least methodologically rigorous in their potential ability to minimize systematic bias:

Randomized controlled trials
Non-randomized controlled trials
Prospective cohort studies
Retrospective case control studies
Cross-sectional studies
Surveillance studies (e.g., using registries or surveys)
Consecutive case series
Single case reports

When there are merely associations but not causal relationships between a study's variables and outcomes, it is important not to draw causal inferences. Confounding refers to independent variables that systematically vary with the causal variable. This distorts measurement of the outcome of interest because its effect size is mixed with the effects of other extraneous factors. For observational, and in some cases randomized controlled trials, the method in which confounding factors are handled (either through stratification or appropriate statistical modeling) are of particular concern. For example, in order to interpret and generalize conclusions to our population of Medicare patients, it may be necessary for studies to match or stratify their intervention and control groups by patient age or co-morbidities.

Methodological strength is, therefore, a multidimensional concept that relates to the design, implementation and analysis of a clinical study. In addition, thorough documentation of the conduct of the research, particularly study selection criteria, rate of attrition and process for data collection, is essential for CMS to adequately assess and consider the evidence.

Generalizability of Clinical Evidence to the Medicare Population

The applicability of the results of a study to other populations, settings, treatment regimens and outcomes assessed is known as external validity. Even well-designed and well-conducted trials may not supply the evidence needed if the results of a study are not applicable to the Medicare population. Evidence that provides accurate information about a population or setting not well represented in the Medicare program would be considered but would suffer from limited generalizability.

The extent to which the results of a trial are applicable to other circumstances is often a matter of judgment that depends on specific study characteristics, primarily the patient population studied (age, sex, severity of disease and presence of co-morbidities) and the care setting (primary to tertiary level of care, as well as the experience and specialization of the care provider). Additional relevant variables are treatment regimens (dosage, timing and route of administration), co-interventions or concomitant therapies, and type of outcome and length of follow-up.

The level of care and the experience of the providers in the study are other crucial elements in assessing a study's external validity. Trial participants in an academic medical center may receive more or different attention than is typically available in non-tertiary settings. For example, an investigator's lengthy and detailed explanations of the potential benefits of the intervention and/or the use of new equipment provided to the academic center by the study sponsor may raise doubts about the applicability of study findings to community practice.

Given the evidence available in the research literature, some degree of generalization about an intervention's potential benefits and harms is invariably required in making coverage determinations for the Medicare population. Conditions that assist us in making reasonable generalizations are biologic plausibility, similarities between the populations studied and Medicare patients (age, sex, ethnicity and clinical presentation) and similarities of the intervention studied to those that would be routinely available in community practice.

A study's selected outcomes are an important consideration in generalizing available clinical evidence to Medicare coverage determinations. One of the goals of our determination process is to assess health outcomes. These outcomes include resultant risks and benefits such as increased or decreased morbidity and mortality. In order to make this determination, it is often necessary to evaluate whether the strength of the evidence is adequate to draw conclusions about the direction and magnitude of each individual outcome relevant to the intervention under study. In addition, it is important that an intervention's benefits are clinically significant and durable, rather than marginal or short-lived. Generally, an intervention is not reasonable and necessary if its risks outweigh its benefits.

If key health outcomes have not been studied or the direction of clinical effect is inconclusive, we may also evaluate the strength and adequacy of indirect evidence linking intermediate or surrogate outcomes to our outcomes of interest.

Assessing the Relative Magnitude of Risks and Benefits

Generally, an intervention is not reasonable and necessary if its risks outweigh its benefits. Health outcomes are one of several considerations in determining whether an item or service is reasonable and necessary. CMS places greater emphasis on health outcomes actually experienced by patients, such as quality of life, functional status, duration of disability, morbidity and mortality, and less emphasis on outcomes that patients do not directly experience, such as intermediate outcomes, surrogate outcomes, and laboratory or radiographic responses. The direction, magnitude, and consistency of the risks and benefits across studies are also important considerations. Based on the analysis of the strength of the evidence, CMS assesses the relative magnitude of an intervention or technology's benefits and risk of harm to Medicare beneficiaries.

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