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The effect of an interactive voice response system on communication of medication and appointment information to patients taking oral anticoagulants

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The effect of an interactive voice response system on communication of medication and appointment information to patients taking oral anticoagulants

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Thesis submitted to the Faculty of Graduate and Postdoctoral Studies in partial fulfillment of the requirements for the MSc Degree in Epidemiology

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1.0 ABSTRACT

Introduction: An interactive voice response system (IVRS) may facilitate communication of medication information to patients taking oral anticoagulants (OAC).

Objective: To evaluate an IVRS for OAC management using a health technology assessment framework.

Design: Quasi-experimental study at the Ottawa Hospital Thrombosis Clinic.

Patients: Patients who had completed 3 months of warfarin therapy, had stable anticoagulation control, and spoke English were enrolled and followed for a minimum of 3 months.

Methods: Patients received their international normalized ratio result, dosage schedule, and date of their next blood test from the IVRS. The IVRS also notified patients of upcoming and missed appointments.

Results: 226 patients were prospectively followed for a mean of 4.2 months. Patients' anticoagulation control during the post-intervention period (80.3%; 95% CI 77.5-83.1) was noninferior to their anticoagulation control during the pre-intervention period (79.9%; 95% CI 77.3-82.6). 77.4% of patients continued using the IVRS after the study. 78% of the scheduled dosage messages were successfully delivered by the IVRS and did not require further input from clinic staff. The IVRS resulted in a minor reduction in the workload of Clinic staff.

Conclusion: An IVRS was a feasible and effective method of communicating medication information in this population of OAC patients. Future work is required to determine the generalizability of these results.

2.0 INTRODUCTION

2.1 Oral anticoagulant management

Oral anticoagulants (OAC) are prescribed to patients with various conditions including atrial fibrillation, mechanical heart valves, and venous thromboembolism.[1] Despite the benefits of OACs, they have potential and serious risks. Studies[2-5] have reported a combined hemorrhagic and thromboembolic rate of 15% per year in OAC patients managed by community practice. Therefore, OAC use must be monitored diligently to maximize the benefits and to minimize the risk of adverse events.

Anticoagulation control is used to assess the quality of OAC use.[6] Anticoagulation control is the proportion of time spent in therapeutic range. It is most appropriately calculated using a patient-time method.[7] Patient-time methods calculate the proportion of days that a patient spends in the therapeutic range. First, all international normalized ratio (INR) results for a patient are arranged chronologically. Then, INR values for days between actual results are determined using an interpolation method. Finally, anticoagulation control is calculated as the number of days with a therapeutic INR divided by the total number of days of observation.

Anticoagulation control is an important outcome because it is associated with both hemorrhagic and thromboembolic events. A meta-analysis[8] of 19 studies that reported INR-specific event rates showed that both hemorrhagic and thromboembolic risk was lowest with an INR of 2 to 3. Compared to an INR range of 2 to 3, INRs below 2 were associated with the highest thromboembolic risk (RR 3.5, 95% CI 2.8-4.4). INRs exceeding 3 were associated with significantly increased hemorrhagic risk (INR 3-5: RR 2.7, 95% CI 1.8-3.9; INR >5: RR 21.8, 95%CI 12.1-39.4). Another meta-analysis[9], which included 71,065 patients, found that approximately 44% (95% CI 39-49) of hemorrhages occurred at INRs above the therapeutic range and 48% (95% CI 41-55) of thromboemboli occurred at INRs below it. These data highlight why optimizing anticoagulation control is important for improving patient outcomes.

Many studies show that anticoagulation control can be poor, especially in the community. The results of a British population-based study[10] of 2,223 OAC patients highlight this point. Jones *et al.*[10] reported that the quartile of patients with the worst anticoagulation control spent 71.6% of the time *outside* the therapeutic range. In a systematic review[11] of 67 studies, the proportion of time spent in therapeutic range by all patient groups was 63.6%. Randomized controlled trials (RCT) and studies based in anticoagulation clinics reported a mean proportion of time in therapeutic range of 66.4% and 65.6%, respectively. In contrast, anticoagulation control in studies from community practice (56.7%) was significantly worse than both RCTs and studies based in anticoagulation clinics. These data show that there is a definite opportunity to improve anticoagulation control, especially among community patients.

Imperfect anticoagulation control is understandable given the difficulty maintaining therapeutic INRs. This is due to two factors. First, the effect of OAC is influenced by many factors including other medications,[12,13] diet,[12-14] and disease.[15,16] Second, anticoagulation management is logistically challenging for both patients and medical staff. A series of steps (Exhibit 9.1) must be executed efficiently for OAC patients to achieve maximum therapeutic benefit. The patient must first attend a laboratory or hospital for an INR blood test. The laboratory or hospital must relay the patient's INR result to the physician responsible for OAC dose management. The physician must then determine if a dose adjustment is required. To do so, the physician must know the patient's target INR range and previous test results. The medication instructions and the date of the next INR test must then be communicated to the patient. The patient continues taking the OAC and the cycle repeats.

Two interventions have attempted to improve steps in the anticoagulation monitoring cycle. First, patient self-management has been used to facilitate INR testing (Step 1 of Exhibit 9.1). Patients who are self-managed avoid having to travel to laboratories for venous sampling by determining their INR results using a capillary whole blood instrument.[2] Dosage is then adjusted by themselves or their physician. Two meta-analyses[17,18] reported that self-management, when compared to standard

monitoring, was associated with significant reductions in all-cause mortality and hemorrhagic and thromboembolic events. These studies also reported improved anticoagulation control for self-managed patients (when measured as a simple proportion of INRs that fell within the therapeutic range). The latter result is difficult to interpret since the self-monitoring group conducted almost 4 times more INR tests then the comparator group.

A second intervention to improve anticoagulation logistics involves a computerized decision support system (CDSS) used for dose adjustment (Steps 3 through 5 of Exhibit 9.1). *DawnAC*, a product of 4S Information Systems Ltd., is an example of such a CDSS. This system keeps a record of each patient's target INR range as well as their INR history. Based on each patient's recent INR result, target INR range, and INR history, the system recommends a weekly dosage schedule and interval to the next INR test. A health care professional approves or changes the *DawnAC* recommendations. A systematic review[19] of CDSSs by Garg *et al.* identified 8 controlled trials that examined the use of CDSSs for monitoring OAC patients. In 5 of those trials, patients who were monitored by a CDSS had better anticoagulation control than patients who received standard monitoring.

Efficiently communicating OAC information to patients is difficult (Step 6 of Exhibit 9.1). Barcellona *et al.*[20] reported that approximately half of the 264 OAC patients in their study reported having practical problems reaching the anticoagulation clinic to collect medication and appointment instructions. Seventy-one percent of the patients in this study[20] stated that they would prefer to receive medication and appointment instructions by fax or phone instead of traveling to the clinic to collect their information. Although a telephone monitoring system is more convenient for patients, it has disadvantages. This system requires health care professionals to relay medication and appointment instructions to patients and handle requests via the telephone. The workload of health care professionals often results in untimely communication of information,[21] especially if they must make several attempts to contact patients.[22]

2.2 Interactive voice response systems

An interactive voice response system (IVRS) may improve communication of OAC information to patients. An IVRS is an information technology that links a person with a computer database via a telephone. Upon each telephone call, the IVRS can deliver medication and appointment instructions while the patient can respond to questions verbally or by pressing the appropriate numbers on the telephone key pad.[23] The IVRS telephone messages are automated and the system can be programmed to continue to call a patient until they have been contacted. Therefore, the delivery of information is not influenced by the workload of health care professionals. Without having to call patients, health care professionals are available for other tasks.

IVRSs are increasingly being used by health care institutions.[24,25] This technology has been used for disease screening (e.g. depression),[26-29] disease symptom monitoring,[30-32] behavior monitoring (e.g. substance abuse),[33-36] conducting behavioral counseling,[37-39] assessing medication adherence,[40,41] and increasing appointment compliance.[42-44] Friedman *et al.*[41] reported that patients monitored by an IVRS for hypertension showed a 6% improvement in mean adherence to antihypertensive medication compared to patients receiving usual care. Feldstein *et al.*[42] demonstrated that patients who received an automated voice message reminder were significantly more likely to complete recommended laboratory monitoring than patients receiving usual care (HR 4.1 95% CI 3.0-5.6). Forster and van Walraven[45] recently highlighted the utility of an IVRS in improving post-discharge monitoring. In summary, the combined features of IVRSs could be used to improve anticoagulation control and reduce the number of adverse events among OAC patients.

A number of health information systems have been used to communicate OAC information to patients.[46-50] Three studies[46-48] have used portable devices that are connected to anticoagulation clinic databases using the internet. The HAT (home automated telemanagement) system[46] records self-monitoring patients' INR results in a home unit device. These data are transmitted to the clinic where a physician reviews the information and forwards their instructions back to the patients' home unit device. The TaoNet system[47] collects INR results of patients at peripheral health units (e.g.

nursing homes), using a portable coagulometer connected to a laptop. The INR results are emailed to the clinic where a physician reviews them and emails their instructions back to the health unit. The TOPCARE system[48] also uses a coagulometer to collect patients' INR results. The coagulometer is connected to the TOPCARE box that sends information to and receives information from the clinic. Two studies[49,51] have used cellular telephone text messaging to monitor OAC patients. TeleWarf[51] and Salvador *et al.*'s "guidance oriented e-service"[49] allow self-monitoring patients to text message their INR results to the clinic and receive their medication instructions in the same way. Lastly, an ongoing study[50,52] is using a web-based system, called INR Online, to communicate with OAC patients. Self-monitored patients log on to the web-based system and record their INR results. A physician reviews the results and records their medication instructions, triggering the system to send an email or cellular telephone text message to the patient.

Compared to these systems of anticoagulation management, an IVRS is primarily appealing because of its generalizability. Patients can be monitored by an IVRS without being self-monitored or requiring email or cellular telephone access. An IVRS called INR RELAY[53] has been used to communicate with OAC patients. INR RELAY was developed in 2000 by staff at the anticoagulant clinic of the Pathology Department in Basildon and Thurrock NHS Trust. On a daily basis, the clinic sends a report of patients' latest medication and appointment instructions to INR RELAY service staff. The service staff then programs the calling system to deliver the automated telephone calls. INR RELAY also calls patients if they miss an INR appointment. In 2000, staff at the clinic conducted an observational study and concluded that both patients and staff were satisfied with INR RELAY.[53] This study had two limitations including no measure of anticoagulation control in patients who used INR RELAY and no measure of the effects that INR RELAY had on the workload of clinic staff.

An IVRS named *CallAssureCDM* was used to communicate with OAC patients. ('CDM' represents 'chronic disease management'.) *CallAssureCDM* is a patented IVRS solution marketed by Vocantas Inc. The study research team, including physicians, pharmacists, nurses, and research staff,

specified the functionality of an IVRS for OAC management. The team also designed the types of automated messages to be delivered to patients and the content of each type of message. Vocantas Inc. developed *CallAssureCDM* according to these specifications. *CallAssureCDM* is unique because it is integrated with the CDSS *DawnAC*. Unlike INR RELAY, *CallAssureCDM* users do not send reports of patients' OAC instructions to service staff who program the calling system. This study is the first to apply *CallAssureCDM* to anticoagulation control.

3.0 OBJECTIVES

3.1 Primary

To determine anticoagulation control of study patients before and after the implementation of the interactive voice response system (IVRS).

3.2 Secondary

3.2.1 To determine the rate of hemorrhagic and thromboembolic events before and after the implementation of the IVRS.

3.2.2 To determine the utility of the IVRS.

3.2.3 To determine the effectiveness of the IVRS's 'Reminder' message.

3.2.4 To determine if patients are satisfied being monitored by the IVRS.

3.2.5 To determine the time and resources required to monitor the IVRS.

4.0 METHODS

4.1 Study design

A quasi-experimental pilot study, using a one-group pretest-posttest design, was conducted[54] A randomized controlled trial (RCT) was unjustified since *CallAssureCDM* had not been used to communicate with oral anticoagulant (OAC) patients. A quasi-experimental pilot study was required to determine the feasibility and effectiveness of this monitoring strategy. A pilot study would highlight the utility of conducting a larger-scale observational study or RCT.[55-57] It would also identify obstacles to implementing a larger study and enable researchers to develop strategies for overcoming those obstacles.[55-58] Lastly, a pilot study would highlight the patient population best suited for *CallAssureCDM*.[59]

A pretest-posttest design was required to compare anticoagulation control of study patients before the implementation of *CallAssureCDM* with their anticoagulation control after the implementation of *CallAssureCDM*. The pre-intervention or pretest period was retrospective, while the post-intervention or posttest period was prospective. Primary data collection was required for the post-intervention period because, as previously mentioned, this study was the first to use this technology.

4.2 Study setting

The study was conducted at the Thrombosis Clinic of the Ottawa Hospital in Ottawa, Ontario. The Clinic monitors approximately 1,200 OAC patients from the Champlain Local Health Integration Network, a large geographical area in Eastern Ontario. Pharmacists, nurses, and clerks at the Clinic are predominantly responsible for patients' routine OAC management. These health care professionals use *DawnAC* version 7.2 to assist in monitoring the large number of patients.

4.3 Study eligibility criteria

Patients were potentially eligible if they had completed 3 months of OAC therapy and had stable anticoagulation control. Patients with a target INR range of 1.5-2.5, 2.0-3.0, or 2.5-3.5 were deemed to have stable control if, in the month prior to recruitment, they had 2 consecutive INR

measurements within therapeutic range. Patients with a target INR range of 3.0-4.0 were assessed using a different criterion because they are at a higher risk of hemorrhagic events.[1] These patients were deemed to have stable control if, in the month prior to recruitment, they had 3 consecutive INR measurements within therapeutic range. Eligibility was not influenced by patient age, duration of OAC therapy, or co-morbidities.

Patients were excluded from the study for any of the following 6 reasons: 1. *CallAssureCDM* only delivers medication instructions to patients taking warfarin; therefore, patients prescribed another type of OAC were ineligible; 2. Patients who did not speak English were ineligible because the *CallAssureCDM* messages have only been recorded in English; 3. Patients who receive calls at a telephone number with an extension were excluded because *CallAssureCDM* is not designed to manage this situation; 4. Patients who had hearing problems were also excluded because the volume of the *CallAssureCDM* messages can not be increased for specific patients; 5. Self-managed patients were excluded since *CallAssureCDM* is not needed to give them their medication instructions; and 6. Patients who could not provide complete follow-up (e.g. were moving outside of Ontario) were ineligible.

4.4 Study recruitment

A pharmacist at the Clinic identified potentially eligible patients from *DawnAC*. I reviewed the list of patients and excluded those who were not taking warfarin. A clerk from the Clinic then contacted the eligible patients to obtain verbal consent for the recruiter to approach them about the study. Since the recruiter was not an employee at the Clinic, the Ottawa Hospital Research Ethics Board (O.H.R.E.B.) requested that patients be initially informed of the study by Clinic staff.

Consenting eligible patients were recruited over the telephone. This was the best method for contacting patients since they typically attend the Clinic less than 4 times per year. Each patient was contacted twice during the recruitment period. During the first recruitment conversation, I spent approximately 10 minutes discussing the study with each patient. If a patient expressed an interest in participating, I mailed them the study package. The study package included a cover letter, an

information sheet, a consent form, and a stamped return envelope for the consent form. The cover letter informed the patient that I would contact them again in 3 to 4 days to further discuss the study. This gave the patient the opportunity to read the information sheet and prepare questions. The information sheet described the study and included my contact number. The consent form was standard and explained the possible benefits and risks of the study. The O.H.R.E.B. requested that a witness sign the consent form to confirm the patient's identity because the patient was recruited over the telephone. Stamped return envelopes were used instead of pre-printed business reply envelopes because they have been shown to be associated with significantly higher response rates.[60]

During the second recruitment conversation, I answered the patient's questions about the study. I also reviewed when they would receive the automated messages, what information the messages would provide, and how to verbally respond to the automated questions. The instructions on how to use *CallAssureCDM* were kept simple.

Patients who agreed to participate in the study were asked to return the signed consent form to the study center. To improve the response rate, I contacted patients a third time if their consent form had not been received.[60] Following receipt of the consent form, the post-intervention observation period started on the day of the patient's first INR test.

4.5 Intervention – *CallAssureCDM*

4.5.1 Configuration

CallAssureCDM is integrated with a *DawnAC* database and a telephone network. *CallAssureCDM* is connected to a *DawnAC* database using a local area network. This connection allows *CallAssureCDM* to identify OAC patients to be contacted and collect the medication information to be delivered to each patient. *CallAssureCDM* is also connected to a hospital's telephone network. This telephone network, a private branch exchange, is linked to the public switched telephone network (PSTN). *CallAssureCDM*'s indirect link to the PSTN enables it to call patients to deliver the appropriate messages.

4.5.2 Installation

CallAssureCDM operates using 2 identical servers (Reliability section 4.5.5) that were stored on hospital premises. Vocantas Inc. technicians worked with Ottawa Health Research Institute (O.H.R.I.) technical support staff to set-up the system. During installation, Vocantas Inc. technicians specified the connectivity settings of *CallAssureCDM* with *DawnAC* and the telephone network.

The Thrombosis Clinic was equipped to handle the technological requirements of *CallAssureCDM*. *CallAssureCDM* was set-up at the Clinic in April 2006.

4.5.3 Administrative tasks

CallAssureCDM administrative tasks are conducted using a web-based interface. The interface is accessible from a computer with Internet Explorer 6, Java, and Windows 2000 Professional, or Windows XP. Administrative tasks include daily monitoring and changing various features of the calling system.

4.5.4 Confidentiality

Access to *CallAssureCDM*'s web-based interface was password protected and patient information stored in the *CallAssureCDM* database was encrypted. Installing *CallAssureCDM* within the Ottawa Hospital's security firewall also ensured patient confidentiality.

4.5.5 Reliability

CallAssureCDM's 2 identical servers are called the 'Primary' and the 'Secondary' servers. The 'Primary' server is responsible for the daily operation of *CallAssureCDM*. The 'Secondary' server monitors the 'Primary' server and becomes operational if the 'Primary' server fails. If this happens, the 'Secondary' server also sends an email notification to Vocantas Inc. technicians. The use of the 2 servers is one of the most complex aspects of *CallAssureCDM*. This set-up, used typically in hardware design, was custom built for the *CallAssureCDM* software.

CallAssureCDM is also monitored by an external server called the 'WatchDog'. This server is stored at Vocantas Inc.'s head office. *CallAssureCDM*'s 'Primary' server is programmed to call the 'WatchDog' every 15 minutes. If the 'WatchDog' does not receive a scheduled call, it sends an

email notification to Vocantas Inc. technicians. The use of both internal and external monitoring systems ensured *CallAssureCDM*'s reliability.

4.5.6 Patient communication: 'Dosage', 'Reminder', and 'Missed' messages

CallAssureCDM communicates with patients using 'Dosage', 'Reminder', and 'Missed' messages. As mentioned in the Interactive voice response system section (section 2.2), the study research team developed these messages. To do so, members of the team first reviewed *DawnAC* to identify the information to be included in each message. This is because the patient data in *DawnAC* dictates the message type and content delivered by *CallAssureCDM*. Next, message dialogues were drafted based on the *DawnAC* data and Vocantas Inc. recorded them. Finally, the team reviewed the recordings of the 3 messages and passed on revisions to Vocantas Inc.

The 'Dosage' message was the most important message. It gave patients their latest INR result, their new weekly dosage schedule, and the date of their next INR appointment. The dosage schedule instructed patients to take a certain number of warfarin tablets of a given strength on each day of the week. For example, "take two 2.5mg tablets according to the following schedule, one on Monday, Wednesday, Friday, and Saturday and 1 and a half on Sunday, Tuesday, and Thursday." The 'Dosage' message also asked patients if they would like to speak with someone from the Clinic and if they had started any new medications. Patients verbally responded to the automated questions with a 'Yes' or 'No' answer. If patients answered 'Yes' to either question, *CallAssureCDM* notified a health care professional to contact the patient.

The 'Reminder' message was developed to help patients attend their scheduled INR appointments. This message notified patients that they had an upcoming INR appointment and indicated the date of the scheduled appointment

The 'Missed' message was developed to inform patients that they missed a scheduled INR appointment. This message was delivered starting the day of the missed appointment and asked the patient to attend a laboratory for an INR test the following day.

4.5.7 Contact recognition

CallAssureCDM can deliver messages to people and answering machines. It uses the answering machine detector (AMD) in the *Intel/Dialogic* telephony board of the 'Primary' server to determine if it has contacted a person or an answering machine. AMD algorithms assess the length of greetings and background noise levels at the beginning of each call. These algorithms are 80-90% accurate.[61] *CallAssureCDM* has been programmed to receive information from the AMD. If a person is contacted, *CallAssureCDM* will ask them to identify themselves as a patient or a primary care-giver of a patient at the Clinic. If the person is correctly identified, *CallAssureCDM* will begin to deliver the message. Otherwise, *CallAssureCDM* will disconnect and attempt to contact the patient or care-giver at a later time. If an answering machine is contacted, *CallAssureCDM* will deliver the complete message.

4.5.8 Speech recognition

Another complex aspect of *CallAssureCDM* is the use of automatic speech recognition (ASR) software. ASR software translates sequences of spoken words into digital data. Using ASR algorithms, the digital data of a particular word or phrase is assigned a value between 0 and 100. This value is the algorithm's 'level of confidence' that the data represents the actual spoken words. *CallAssureCDM*'s messages proceed based on the algorithm's level of confidence and the digital data. If the level of confidence is less than or equal to 50, *CallAssureCDM* will repeat the previous question or statement. If the level of confidence is greater than 50, *CallAssureCDM* will proceed according to the digital data. Vocantas Inc. selected the threshold of 50 based on previous testing by their company.

4.5.9 Activation

CallAssureCDM was activated for individual patients using 3 independent fields in *DawnAC* (version 7.2 and later). The fields are titled 'Send dosing instructions', 'Send reminders', and 'Send did not attend follow-up'. The 'Send dosing instructions' field corresponds to the 'Dosage' message, the 'Send reminders' field corresponds to the 'Reminder' message, and the 'Send did not attend

follow-up' field corresponds to the 'Missed' message. When an 'X' was placed in any of the three fields, *CallAssureCDM* extracted the necessary information from *DawnAC* and called the patient to deliver the appropriate message. These fields, found in the 'Letters' tab, were important because they enabled *CallAssureCDM* to distinguish between 'CallAssure' and 'non-CallAssure' patients.

4.5.10 Calling report

The details of calls were documented in the 'Report' section of the web-based interface. Each row in the 'Report' represented 1 attempt to contact a patient. For each attempt, *CallAssureCDM* recorded the unique call and patient identifier, the patient's name, the type of message delivered ('Dosage', 'Reminder', or 'Missed'), the date/time of the call, the type of contact (person, answering machine, no answer, busy, other, or low recognition error), the duration of the call, and the result of the call (success or failure). Users could generate reports for a given time period, export the data to an Excel spreadsheet, and save the new file.

4.5.11 User defined features

CallAssureCDM has a number of features that allow the user to customize it to their needs. These features are in the 'Call' and 'Call Schedules' sections of the web-based interface. The possible options for each feature are described below. The options that were used during this study have also been identified.

4.5.11.1 Calling windows

Users specify the time periods that *CallAssureCDM* attempts to contact patients. These time periods are referred to as calling windows. A calling window is selected for every day of the week for each message type. If a calling window is not specified for a given day, *CallAssureCDM* will not contact patients on that day.

CallAssureCDM was programmed to deliver the 'Dosage' message from Monday to Friday between 9:00am and 9:00pm. The large calling windows were selected to increase the likelihood of patients receiving their medication and appointment information on the same day as their INR test. *CallAssureCDM* calls the patient to deliver the 'Dosage' message immediately after the pharmacist

has approved the patient's latest INR result and scheduled them for an upcoming appointment. Calling windows for the 'Dosage' message were not selected for Saturday and Sunday because patients do not have INR tests on the weekend.

CallAssureCDM was programmed to deliver the 'Reminder' message from Monday to Sunday between 9:00am and 9:00pm.

Initially, *CallAssureCDM* was programmed to deliver the 'Missed' message between 7:00pm and 9:00pm starting the day of the missed appointment. *CallAssureCDM* would continue to deliver the message every day until the Clinic received the patient's INR result. If a patient had their INR test before 10:00am, as directed by the Clinic, the Clinic forwarded the medication and appointment instructions to the patient before 7:00pm that day. One month into the study, I received a number of calls from patients who received 'Missed' messages and requested that this feature be deactivated. To satisfy these patients, I changed the calling windows so that the message was only delivered on Tuesday, Thursday, and Sunday.

4.5.11.2 Message salutation

CallAssureCDM can deliver 2 types of message salutations. The salutation can address the patient by name or ask them if they are a patient or a primary care-giver of a patient at the Clinic. To ensure patient confidentiality, patient names were not used in the 3 messages.

4.5.11.3 Notification to contact patients

As mentioned in the Patient Communication section (section 4.5.6), a patient was contacted by a health care professional if they requested to speak with someone from the Clinic or indicated that they started new medications during the 'Dosage' message. *CallAssureCDM* can notify a health care professional to contact patients in 2 ways. It can transfer the 'Dosage' call directly to Clinic staff or send an email to staff. During this study, health care professionals were notified to contact patients by email. To ensure patient confidentiality, the email only contained patients' unique identifier.

Unfortunately, there were problems with the email notification during the study. Although *CallAssureCDM* was correctly recording patients' requests to be contacted, it was not sending the email to Clinic staff. To resolve this issue, Vocantas Inc. added a new section to the web-based interface called 'Requests'. Each row in this section represents 1 request. For each request, *CallAssureCDM* recorded the patient's unique identifier, the patient's name, and the date/time of the request. Although the email notification was fixed before the end of the study, both features were used to ensure reliability.

4.5.11.4 Answering machine messages

CallAssureCDM can be programmed to leave 'complete' or 'notification' messages on patients' answering machines. 'Complete' messages give patients their medication and appointment information. 'Notification' messages instruct patients to contact the Clinic to collect this information. During the recruitment period, more than 70% of patients requested that their information be left on their answering machine. Therefore, *CallAssureCDM* was programmed to leave 'complete' messages.

4.5.11.5 Patient contact attempts

Users specified the number of attempts *CallAssureCDM* could make to contact patients. *CallAssureCDM* reattempted to contact patients if previous attempts were recorded as a failure in the 'Report'.

At the start of a calling window, *CallAssureCDM* scans *DawnAC*, compiled a list of patients to be contacted, and called them one after the other. If a call was unsuccessfully delivered, the patient was added to the 're-attempt' list. *CallAssureCDM* then called those patients. Patients who had been successfully contacted were removed from this list, while patients who have not been contacted were called again.

CallAssureCDM was programmed to make 3 attempts to contact patients. This feature applies to all 3 types of messages.

4.5.11.6 'Reminder' message feature

Users selected the number of days before the scheduled INR appointment that patients received the 'Reminder' message. *CallAssureCDM* was programmed to deliver the 'Reminder' message 2 days before the appointment. During the recruitment period, patients indicated that an earlier reminder would give them more time to make transportation arrangements.

4.5.11.7 'Missed' message feature

As mentioned in the Patient Communication section (section 4.5.6), the 'Missed' message instructed the patient to attend a laboratory for an INR test the following day. *CallAssureCDM* users specified the time of day that the patient is instructed to arrive at the laboratory. *CallAssureCDM* was programmed to instruct patients to arrive at the laboratory before 10:00am. If a patient attended the laboratory before 10:00am, the laboratory forwarded the patient's INR result to the Clinic before noon. The pharmacist was then able to process the result and pass on the medication and appointment information to the patient before the end of the day.

4.5.12 Implementation of *CallAssureCDM* at the Thrombosis Clinic

In April 2006, the *CallAssureCDM* servers were set-up at the Clinic. They were not connected with *DawnAC* or the Clinic's telephone network at this time. It was not until August 2006 that the necessary hospital approvals were in place to conduct the study. In August, Dr. Alan Forster, Dr. Marc Rodger, and I met with O.H.R.I. technical support staff to discuss the proposed study. The goals of the project and technical requirements of *CallAssureCDM* were described. After agreeing to assist with the study, the technical support staff worked with Vocantas Inc. to connect *CallAssureCDM* to *DawnAC* and the Clinic's telephone network. At this time, the Clinic was using *DawnAC* version 7.1.

The post-intervention period was initially scheduled to start on January 1, 2007. *CallAssureCDM* was activated for study patients on December 31, 2006 since Vocantas Inc. indicated that the system could be activated for patients at any time. Unfortunately, after doing so a problem was identified. *CallAssureCDM* immediately began calling study patients to deliver the

medication information from their last INR test, some of which had been processed 4 weeks prior. This problem was resolved by activating *CallAssureCDM* for study patients after the pharmacist processed their first study INR result.

Four days after turning on *CallAssureCDM*, a second problem was identified that resulted in the study being stopped. Newly added patients to *DawnAC* who were dosed by the pharmacist for the first time received the 'Dosage' message from *CallAssureCDM*. None of these patients had been approached to participate in the study. This problem was the result of the original design of *CallAssureCDM*.

Vocantas Inc. designed *CallAssureCDM* to identify all patients in a clinic's *DawnAC* database as 'CallAssure' patients. To deactivate *CallAssureCDM* for a patient, users had to access the web-based interface and highlight the patient in the 'Exclusion List'. Newly added patients to *DawnAC* were called because *CallAssureCDM* users were unable to highlight these patients in the 'Exclusion List' before *CallAssureCDM* extracted their information from *DawnAC* and called them.

Due to time and cost commitments, Vocantas Inc. did not change the design of *CallAssureCDM* to resolve this issue. The only way for us to resolve this problem was to upgrade from version 7.1 of *DawnAC* to version 7.2. As discussed in the Activation section (section 4.5.9), version 7.2 includes the 3 *CallAssureCDM* activation fields for individual patients.

Unfortunately, the manufacturer of *DawnAC* did not release version 7.2 until two months after the proposed study start. When version 7.2 was available, the *DawnAC* administrator at the Clinic worked with the manufacturer of *DawnAC* and O.H.R.I. technical support staff to perform the upgrade.

In mid-March 2007, members of the study research team tested *CallAssureCDM* to ensure that it worked properly with the new version of *DawnAC*. Fake patients were created in *DawnAC*, each having the telephone number of a member of the team. On multiple occasions, the pharmacist dosed the fake patients and *CallAssureCDM* delivered the 'Dosage' messaged. Members of the team also received the 'Reminder' and 'Missed' messages. During this testing phase, team members

identified sections of the messages that required improvement and worked with Vocantas Inc. staff to finalize the message scripts. In April 2007, Vocantas Inc. hired a professional recording company to record the finalized scripts that were used during the study. Approximately 150 scripts were recorded to provide instructions for the range of possible INR test results, dosage schedules, and appointment dates.

CallAssureCDM was fully operational at the beginning of May 2007. This study was approved by the Ottawa Hospital Research Ethics Board from July 28, 2006 to July 28, 2008 (Appendix 1).

4.6 Patient schedule of events

4.6.1 Routine OAC management

The post-intervention period started on the day of a patient's first INR following receipt of the consent form. The 3 *CallAssureCDM* fields were activated for each study patient after the pharmacist processed their INR result. Therefore, the first automated call received by patients was the 'Dosage' message. The *CallAssureCDM* fields in *DawnAC* remained activated until patient follow-up was complete.

During the post-intervention period, patients were followed for a minimum of 3 months. During that time, they attended regular appointments at the laboratory of their choice for venous blood sampling (Step 1 of Exhibit 9.2). Their INR results were forwarded to the Clinic and processed as usual (Steps 2 through 6 of Exhibit 9.2). *CallAssureCDM* then called patients to deliver the 'Dosage' message (Steps 7 and 8 of Exhibit 9.2). *CallAssureCDM* also called patients to deliver the 'Reminder' and 'Missed' messages, if applicable (Step 9 of Exhibit 9.2). At the end of the study, patients were contacted to discuss *CallAssureCDM*. If patients chose to continue with *CallAssureCDM* after the 3-month period, their observation period was extended.

4.6.2 Post-study semi-structured telephone interview

A semi-structured interview was developed to collect patient feedback on *CallAssureCDM*. Vocantas Inc. does not systematically collect patient feedback on their products. Therefore, it is the

responsibility of the health care institution to evaluate its patients' experience with the new technology.

Semi-structured interviews were used to elicit patient feedback about *CallAssureCDM*. Semi-structured interviews are conducted using a pre-determined list of topics and questions.[62] Interviewers address topics and ask open-ended questions to promote discussion with interviewees.[63,64] It is common for interviewers to ask unplanned questions throughout the conversation.[62] Semi-structured interviews may be tape-recorded or documented in writing by the interviewer. Interviewee feedback is coded and then analyzed to identify recurring themes.[65] Semi-structured interviews are very appropriate method for collecting patient feedback on newly introduced health services.[62,66,67] They allows patients to describe, in their own words, their experience with the new service. Semi-structured interviews have also been shown to yield more comprehensive and complete data than surveys.[68,69] This is because interviewers are able to clarify patients' responses and ensure that all data is collected before the interview is complete.[62,70]

I conducted the interviews by telephone on the last day of the 3-month post-intervention observation period. Telephone interviews are cost and time effective [67,71-73] and were the most feasible means of collecting patient feedback for this study. Also, studies have shown that telephone interviews have higher response rates than postal surveys[65,67,75] and comparable response rates to face-to-face interviews.[63,75] Patients who withdrew or were removed from the study were contacted shortly after their last day of observation. Patients were called until they had been contacted.

The pre-determined list of interview topics for the interview included message clarity, ease of interacting with the automated dialogue, and message usefulness. After introducing each topic, the interviewer asked patients to describe their experience with respect to that topic. Each topic was discussed 3 times; once for each message type. If a patient requested not to receive the 'Reminder' and 'Missed' messages, the interviewer only discussed the 'Dosage' message. At the end of the conversation, patients were given the option to continue with *CallAssureCDM* or return to the Clinic's standard communication system.

4.7 Monitoring responsibilities

4.7.1 Natalie Oake

A potential advantage of *CallAssureCDM* is the reduction in time that staff spends contacting patients. However, *CallAssureCDM* must be monitored on a daily basis to ensure that it functions properly and that patients receive their medication information.

I was responsible for monitoring *CallAssureCDM* and performed several daily tasks. At least once a day, I reviewed the new records in the 'Report' table and contacted patients whose 'Dosage' messages were unsuccessfully delivered. I also contacted patients who requested to speak with someone from the Clinic or indicated that they started taking new medications. Frequently, I transferred these patients to speak with the pharmacist. Patients whose 'Reminder' and 'Missed' messages were unsuccessfully delivered were not contacted because these calls are not standard practices of the Clinic.

I was also responsible for contacting Vocantas Inc. technicians when a problem with *CallAssureCDM* was identified.

4.7.2 Pharmacist

The pharmacist's main responsibility was contacting study patients whose INRs were excessively low (0.5 less than their low target INR) or high (0.5 greater than their high target INR). The pharmacist also performs this task for non-study patients. The pharmacist contacted patients to investigate if they had changed their diet, started new medications, or had other possible explanations for the out-of-range INR result. To prevent *CallAssureCDM* from contacting the patients first, the pharmacist would review the patients' INR result but not completely process it in *DawnAC*. After speaking with the patient, the pharmacist would complete their record in *DawnAC* and *CallAssureCDM* would call them. This method may seem redundant since patients received their medication instructions twice. However, it was more safer than de-activating the 'Send dosing instructions' field for the current INR result and re-activating it after the subsequent INR result since it avoided the situation where I or the pharmacist forgot to re-activate the 'Dosage' message.

For Clinic staff to easily identify study patients in *DawnAC*, the Clinic used the 'Preferred Clinic' field in the Patient interface. The *DawnAC* administrator at the Clinic created 2 possible values for this field. 'Parkdale' represented standard monitoring by the Clinic (on Parkdale Avenue) and 'CallAssure' represented a study patient. The 'Preferred Clinic' field, unlike the 3 *CallAssureCDM* activation fields in the Letters tab, was not connected with *CallAssureCDM*.

4.7.3 Vocantas Inc.

The main responsibility of the technicians from Vocantas Inc. included responding to the email notifications from the 'Secondary' and 'WatchDog' servers that indicated technical problems (Reliability section 4.5.5). They also responded to problems identified by the research team. Technicians investigated the problems by connecting to *CallAssureCDM*'s 'Primary' and 'Secondary' servers.

4.8 Data management

A database was created in *Microsoft Office Access 2003* to manage study data. The database contained 5 tables that documented patient demographics, OAC therapy information, recruitment information, a copy of the *CallAssureCDM* calling 'Report', and post-study interview responses. Patient demographics and OAC therapy information were extracted from *DawnAC*. The OAC information included start date of OAC therapy; indication for warfarin; target INR range; INR dates and results; and hemorrhagic and thromboembolic events. The Clinic identifies outcome events (i.e. hemorrhagic and thromboembolic events) through patient reporting. I manually entered the recruitment information and post-study interview responses in the database. Records from the 'Report' were copied and appended to the database. The database was especially helpful for monitoring *CallAssureCDM* on a daily basis. Users were able to document follow-up phone calls to patients whose messages were not delivered. I was the only person who had access to the study database.

4.9 Study evaluation

CallAssureCDM was evaluated using a health technology assessment framework. Steuten *et al.*[76] presented this framework in a systematic review and proposed that the framework be used to assess 3 types of disease management programs including educational (aimed at patients), professional (aimed at health care professionals), and organizational (designed to improve the way in which care is delivered) programs. These programs are assessed using a combination of outcome, process, and structure indicators. Outcome indicators describe clinical outcomes and patient satisfaction outcomes; they also detail the cost of implementing and monitoring the technology. Process indicators describe the changes in workflow of health care professionals as a result of implementing the technology. Lastly, structure indicators describe the setting in which the technology is used and the resources required to support the technology.

CallAssureCDM is an example of an organizational disease management program. Specifically, it is designed to improve the way in which patients receive their OAC medication information. As suggested by Steuten *et al.*, outcome, process, and structure indicators were used to comprehensively evaluate *CallAssureCDM*.

4.9.1 Outcome indicators

Five outcome indicators were used to evaluate *CallAssureCDM*. First, anticoagulation control of patients during the post-intervention period and in the pre-intervention period was determined. This was the primary outcome of the study. Secondly, the rate of hemorrhagic and thromboembolic events during the post-intervention period and in the per-intervention period were calculated. Third, patient satisfaction with *CallAssureCDM* was assessed. This was measured as the proportion of eligible patients who continued with *CallAssureCDM* after the study. To further assess patient satisfaction, patient responses from the post-study interview were summarized. Fourth, the effectiveness of the 'Reminder' message was determined. Effectiveness was defined as the proportion of INR appointments that were attended during the post-intervention period. It was

assumed that a patient attended the scheduled appointment if the Clinic received their INR result less than 2 days after the appointment. Lastly, the cost of purchasing *CallAssureCDM* was detailed.

4.9.2 Process indicators

Two process indicators were used to evaluate *CallAssureCDM*. First, the overall utility of the calling system was captured. Utility was defined as the proportion of scheduled 'Dosage' messages that were successfully delivered by *CallAssureCDM* and did not require further input from Clinic staff. Secondly, the time required to monitor *CallAssureCDM* on a weekly basis was assessed.

4.9.3 Structure indicators

Two structure indicators were used to evaluate *CallAssureCDM*. First, the characteristics of the study population were compared to the characteristics of the Clinic population. Secondly, the resources required to implement *CallAssureCDM* on a permanent basis were described.

4.10 Analyses

All analyses were conducted using *SAS* version 9.1 (SAS Institute; Cary, NC).

4.10.1 Outcome indicators

4.10.1.1 Anticoagulation control

Three steps were used to determine anticoagulation control. First, linear interpolation[77] was used to calculate INR values for days between actual measurements. Second, the mean proportion of days in therapeutic range was calculated for each patient. Finally, the overall mean (i.e. the mean of patient means) was calculated along with 95% confidence intervals. These steps were applied to the pre-intervention and post-intervention data.

Linear interpolation[77] is the standard method of estimating anticoagulation control. A systematic review[11] reported that 54 (80.6%) of 67 studies that measured anticoagulation control using a patient-time method used linear interpolation. An advantage of linear interpolation is that it accounts for patient-time. However, a limitation of this method is that it increases the number of INR measures and, consequently, results in an inappropriately precise estimate of the mean proportion of days in therapeutic range and associated confidence interval.[7]

It was determined if patients' anticoagulation control during the post-intervention period was noninferior to their anticoagulation control during the pre-intervention period. First, a margin of noninferiority was selected. To do so, the minimum clinical important differences (MCID) reported by published RCTs where anticoagulation control was the primary outcome were captured. The smallest MCID of anticoagulation control identified was an absolute difference in proportion of time in therapeutic range of 10%. This MCID was cited in 5 RCTs.[78-82] Based on these data, a margin of noninferiority of 5% was selected since it is recommended that the margin of noninferiority is smaller than the standard MCID.[83] This conservative margin of non-inferiority was also chosen to account for the inappropriately precise estimate of anticoagulation control. Secondly, a paired t-test was used to calculate the mean difference in anticoagulation control between the pre and post-intervention periods as well as the 2-sided 95% confidence intervals for the difference.[84] This test was appropriate because the pre-intervention and post-intervention samples were not independent.[84] Lastly, the mean difference and corresponding 95% confidence interval were compared to the margin of noninferiority (5%) and a null effect. If the 95% confidence interval of the mean difference crossed zero and did not include the margin of noninferiority, it could be concluded that patients' anticoagulation control during the post-intervention period was noninferior to their control during the pre-intervention period.[83,84]

4.10.1.2 Hemorrhagic and thromboembolic event rates

To determine the rates of hemorrhagic and thromboembolic events, the total number of each type of event was divided by the total observation time for both the pre-intervention and post-intervention periods.

4.10.1.3 Patient satisfaction

First, the proportion of eligible patients who continued with *CallAssureCDM* after the post-intervention period were descriptively analyzed. Second, logistic regression[85] was used to investigate if patient factors (including gender, age, indication for OAC use, target INR range, and duration of

OAC use) were associated with whether a patient chose to continue with *CallAssureCDM*. Lastly, patient responses from the post-study interview were descriptively analyzed.

4.10.1.4 Effectiveness of the 'Reminder' message

The proportion of INR appointments that were attended during the pre and post-intervention periods were determined using *DawnAC* data. Two *DawnAC* dates were compared: the date of the scheduled INR appointment and the date the pharmacist processed the patient's INR result. As indicated in the Outcome indicators section (section 4.9.1), it was assumed that a patient attended the INR appointment if the pharmacist processed their result less than 2 days after the scheduled appointment date. The proportions from the 2 time periods were compared using a chi-square test.

Unfortunately, there is a problem with the *DawnAC* data. When the pharmacist approves a patient's INR result in *DawnAC* and schedules them for the next appointment, the date of the upcoming appointment is saved in a new record in *DawnAC*. However, that record is deleted and replaced with a new record and new date if the patient missed the original appointment by approximately a week. Consequently, the proportion of attended INR appointments is biased towards a higher attendance rate.

To investigate the accuracy of the *DawnAC* data, a sensitivity analysis was conducted. The 'Report' data in the post-intervention period was used to measure the proportion of INR appointments that were attended during the post-intervention period. It was assumed that a patient attended an appointment if a 'Dosage' message was delivered 2 or 3 days after a 'Reminder' message. Recall that *CallAssureCDM* was programmed to deliver the 'Reminder' message 2 days before patients' INR appointments (section 4.5.11.6). If a patient requested not to receive the 'Reminder' message, their record in *DawnAC* was frequently reviewed to determine if they attended their appointments.

4.10.1.5 Cost of purchasing *CallAssureCDM*

The cost of purchasing *CallAssureCDM* was detailed.

4.10.2 Process indicators

4.10.2.1 Overall utility of *CallAssureCDM*

The "Report" data was used to determine the overall utility of *CallAssureCDM* for all study patients. A subgroup analysis using Poisson regression[86] was conducted to determine if *CallAssureCDM* was more useful for patients of a certain age. The dependent variable in the regression model was the number of messages per patient that were successfully delivered by *CallAssureCDM* and did not require further input from Clinic staff. The independent variable was age and the offset variable was the log of the total number of messages to be delivered to each patient. The model was generated in SAS using PROC GENMOD.

4.10.2.2 Time required to monitor *CallAssureCDM*

Three steps were used to determine the time required to monitor *CallAssureCDM* on a weekly basis. First, the time required to perform each monitoring task for every week of the study was determine. The mean weekly time required to perform each task was then calculated. Finally, the means were summed to calculate the total time required to monitor *CallAssureCDM* during the study.

4.10.3 Structure indicators

4.10.3.1 Comparison of study population with Clinic population

The characteristics (e.g. age, duration of OAC therapy) of the Clinic population were descriptively analyzed.

4.10.3.2 Resources required

The resources required to implement *CallAssureCDM* were detailed.

4.10.4 Sample size calculation

The sample size for the study was determined by the desired precision of the primary outcome, anticoagulation control.[87] The following formula was used to calculate the sample size: $N=(4s^2/d)$. This formula is applicable when the outcome is a mean based on a single sample. The formula included a value for the expected standard deviation (s) of anticoagulation control and the

desired confidence interval width (d). An expected standard deviation estimate of 30.1 and a 95% confidence interval width of 8 were used. The standard deviation estimate was reported by van Walraven *et al.*[88] in a population-based study of 7,179 OAC users. A total of 226 patients were required for the study.

4.11 Conflict of interest statement

No member of the research team or staff at the Clinic has a financial vested interest in Vocantas Inc. or *CallAssureCDM*. None of the research staff was paid by Vocantas Inc. to conduct the study. Vocantas Inc. supplied the *CallAssureCDM* application and technical support free of charge for the study.

5.0 RESULTS

5.1 Patient recruitment

Patients were recruited between November 23, 2006 and August 1, 2007. During the recruitment period, the Thrombosis Clinic identified 357 patients who had completed 3 months of oral anticoagulant (OAC) therapy, had stable anticoagulation control, and were taking warfarin (Exhibit 9.3). Two of these patients requested not to be contacted by the recruiter. Therefore, 355 patients were approached for potential study participation. Forty-one patients were excluded because: they discontinued warfarin before the study started (N=24); resided outside of Ontario during the study period (N=8); had hearing problems (N=3); developed unstable anticoagulation control (N=2); received their warfarin dosing instructions at a telephone number with an extension (N=2); did not speak English (N=1); or started self-managing their warfarin dosage before the study period (N=1). Eighty-eight patients declined to participate because they were satisfied with the existing monitoring system (N=36), preferred not to participate in a research study (N=15), or other reasons (N=8). The remaining 29 patients who declined to participate did not provide a reason.

Two hundred twenty-six patients were enrolled in the study. Four of these patients only agreed to enroll if they did not receive the 'Reminder' and 'Missed' messages. They believed that these messages were unnecessary and would be an annoyance.

It took 150 hours (mean of 25 minutes per patient) to enroll the 226 patients. This included contacting the 355 patients to conduct the first recruitment conversation, mailing the study package to interested patients, and contacting the interested patients a second time to answer their questions about the study. On average, 2 calls were required per patient to contact them for the first recruitment conversation. During these conversations, 274 patients expressed an interest in participating in the study and were mailed the study package. Twenty-two of those patients either did not receive the mailed package or misplaced it and requested to receive a second one. A total of 296 study packages were mailed to patients.

5.2 Patient characteristics

Approximately half of the 226 patients were female. The median age was 58 years (Interquartile range 48-68, range 21-88) (Exhibit 9.4). By far, the most common indication for warfarin was venous thromboembolism (79.2%), followed by atrial fibrillation (3.1%), and mechanical heart valves (2.2%). Nearly all patients (92.5%) had an INR target range of 2.0-3.0. Approximately half of the patients started warfarin between 1 and 5 years before the study and approximately a third of the patients had been taking warfarin longer than 5 years. Unfortunately, patient co-morbidities were not captured in *DawnAC* and are, therefore, not available for this analysis. The study population was similar to all other patients monitored by the Clinic with respect to the characteristics captured. The comparisons between the 2 populations are detailed in section 5.4.3.1.

5.3 Patient follow-up

Patient follow-up for the post-intervention period began on May 7, 2007 and ended on December 14, 2007. The 226 patients were prospectively followed for a total of 78.5 years, with a mean follow-up of 4.2 months (SD 1.8 months; range 1 day to 7.2 months).

One hundred ninety-three patients (85.4%) completed the 3-month post-intervention observation period (Exhibit 9.3). Fourteen patients (6.2%) were removed from the study because they discontinued warfarin (N=8), stopped being monitored by the Clinic (N=4), or had comprehension problems during the study (N=2). An additional 19 patients (8.4%) withdrew from the study because they found the automated instructions confusing (N=11) or too fast (N=6); or they missed the personal contact with Clinic staff (N=2).

5.4 Evaluation of *CallAssureCDM*

5.4.1 Outcome indicators

5.4.1.1 Anticoagulation control

Patient anticoagulation control during the post-intervention period was noninferior to their anticoagulation control during the pre-intervention period (Exhibit 9.5). With the interactive voice

response system (IVRS), patients were in the therapeutic range 80.3% of the time (95% CI 77.5-83.1). In the pre-intervention period, patients spent 79.9% of the time in therapeutic range (95% CI 77.3-82.6). The mean difference in anticoagulation control between the pre and post-intervention periods was 0.36% (95% CI -2.95-3.67). Patients' post-intervention anticoagulation control was noninferior because the 95% confidence interval of the mean difference includes zero and excludes the margin of noninferiority (5%).

5.4.1.2 Hemorrhagic and thromboembolic event rates

No study patient had a hemorrhagic or thromboembolic event during the pre or post-intervention periods. Therefore, the hemorrhagic and thromboembolic event rates were 0% per year for both study periods.

5.4.1.3 Patient satisfaction

The majority of patients were satisfied with *CallAssureCDM*. One hundred sixty-four patients chose to continue with *CallAssureCDM* after the post-intervention period (Exhibit 9.6). This represents 77.4% of the patients eligible to continue with *CallAssureCDM* after excluding the 14 patients who were removed from the study for reasons listed in section 5.3. The 2 most common reasons why patients continued using *CallAssureCDM* included: the calling system delivered clear and timely information (N=86); and the patients believed that the system decreased the workload of Clinic staff. Twenty-nine patients (13.7% of eligible patients) chose not to continue with *CallAssureCDM* after the post-intervention period. Their primary reasons for not continuing included: they missed the personal contact with Clinic staff (N=12); they found the automated instructions confusing (N=7) and too fast (N=5); and recognitions problems with their answering machine (N=5).

Based on the logistic regression model, the only factor that was significantly associated with continuing with *CallAssureCDM* was age (OR 0.96 95% CI 0.93-0.99). As patient age increased, the likelihood of continuing with *CallAssureCDM* decreased.

All patients provided feedback on *CallAssureCDM* during the post-study interview (Exhibit 9.7). Overall, patients were satisfied with the 'Dosage' message. Approximately three-quarters of patients found the instructions easy to understand and the automated dialogue easy to interact with. Patients who had problems with the 'Dosage' message provided 5 suggestions for its improvement. The two most common suggestions included slower instructions and re-phrasing the first question of the automated dialogue. Rather than asking "Are you a patient or the primary caregiver of a patient at the Thrombosis Clinic?", patients suggested the message salutation be changed to "Please answer 'Yes' if you are a patient or the primary caregiver of a patient at the Thrombosis Clinic". Patients also suggested including a notification sentence before the weekly dosage schedule. For example, *CallAssureCDM* could inform patients that "there is no change in your weekly dosage schedule" or "your weekly dose has increased/decreased". This would alert patients that they have to copy down new dosing instructions. Although the dosing schedule instructs patients to take tablets of a certain strength, a number of patients were not comfortable receiving their dosing schedule in "tablets per day" and suggested that the instructions be given both in tablets per day and milligrams per day. Lastly, patients suggested that the 'Dosage' message provide the contact number for the pharmacist at the Clinic. They felt that this would be especially helpful when the 'Dosage' message is left on patients' answering machines.

Patients were very satisfied with the 'Reminder' message. Ninety-five percent of patients who received the 'Reminder' message found the instructions easy to understand and the dialogue easy to interact with. Patients who had problems with this message suggested that it could be improved by decreasing the speed of the dialogue. Three-quarters of patients who received this message reported that it was helpful in keeping their appointments. The remaining 25% of patients claimed to be diligent with their appointments and found this message unnecessary.

Compared to the 'Dosage' and 'Reminder' messages, patients were less satisfied with the 'Missed' message. A third of the patients who received this message reported that it gave them incorrect information (i.e. the message indicated that they missed an appointment when they actually

did not). Recall that *CallAssureCDM* delivers the 'Missed' message between 7:00pm and 9:00pm on Tuesday, Thursday, and Sunday. Therefore, patients receive this message even if they had their INR test after 10:00am on these days. A number of patients remarked on the potential of this message, but indicated that the timing of the calls must be improved for the message to be useful. Half of the patients who received the 'Missed' message reported that it was helpful to be informed of the missed appointment. The other half reported that it was an annoyance since they missed the appointment due to other commitments and not because they forgot about it.

5.4.1.4 Effectiveness of the 'Reminder' message

The proportion of appointments attended during the post-intervention period was the same as the proportion attended in the pre-intervention period (Chi-square value = 0.0013, $p>0.05$, df=1). During the post-intervention period, patients attended 1,429 (91.8%) INR appointments out of a total of 1,557. On average, each patient attended 91% of their appointments. Sixty-four percent of patients attended all appointments, 22% missed 1 appointment, 10% missed 2 appointments, and 4% missed 3 or more appointments. There was no relationship between the number of appointments attended and patients' satisfaction with the 'Reminder' message. During the pre-intervention period, patients attended 797 (91.8%) INR appointments out of a total of 868. On average, patients attended 89% of their appointments. The majority of patients (71.2%) attended all appointments. Twenty-six percent of patients missed 1 appointment and only 2.8% missed 2 appointments.

The sensitivity analysis, which used the likely more complete 'Report' data, yielded somewhat different results. This methodology determined that patients in the post-intervention period attended 1,322 (84.9%) INR appointments out of 1,557. On average, each patient attended 83% of their appointments. Forty-six percent of patients attended all appointments, 28% missed 1 appointment, 15% missed 2 appointments, and 11% missed 3 or more appointments. The sensitivity analysis identified 107 missed appointments that were not identified using the *DawnAC* data.

5.4.1.5 Cost of purchasing *CallAssureCDM*

The cost of purchasing *CallAssureCDM* is approximately $90,000. A hospital or clinic must also pay an additional $46,000 per year for technical support from Vocantas Inc..

5.4.2 Process indicators

5.4.2.1 Overall utility of *CallAssureCDM*

CallAssureCDM was useful to communicate medication information to patients (Exhibit 9.8). During the post-intervention period, 1,557 'Dosage' messages were scheduled to be delivered. One thousand two hundred eleven of those messages (77.8%) were successfully delivered by *CallAssureCDM* and did not require further input from Clinic staff. Input from Clinic staff was required for 346 messages (22.2%) because: the patient had an excessively low or high INR result (N=143); the message was unsuccessfully delivered by *CallAssureCDM* after 3 attempts (N=128); the patient requested to be contacted by Clinic staff (N=48); or the message was recorded as being successfully left on the patient's answering machine, but the patient subsequently stated they did not receive the message (N=27). Overall, the IVRS was unable to deliver the message 10% of the time.

5.4.2.1.1 Details of *CallAssureCDM* utility

Eighty-four patients had 143 low or high INR results that required an intervention by the pharmacist. None of these patients was removed from the study due to unstable anticoagulation control.

Seventy-five percent of 'Dosage' messages were successfully delivered after the 1st contact attempt (Exhibit 9.9). Following the 2nd and 3rd attempts, the overall proportion of successfully delivered messages increased to 87% and 92%, respectively. Although the 2nd and 3rd attempts improved the overall proportion of successfully delivered messages, only half of the 2nd contact attempts and a third of the 3rd contact attempts were successfully delivered.

It is noteworthy that 15% of the 1st contact attempts failed when a person was contacted. These calls may have failed because the patient or caregiver was not identified or the patient had problems with the automated dialogue and hung up the telephone. Based on patient responses from

the post-study interview (section 5.4.1.3), I suspect that a large proportion of these calls failed as a result of patients having problems with the dialogue.

Forty-four patients requested to be contacted by Clinic staff 48 times. Most commonly, patients requested to speak with the pharmacist (N=16) to discuss new medications, changes in diet, or their latest INR result. The other reasons for requesting to be contacted included changing their next INR appointment date (N=10), clarifying their medication instructions (N=9), renewing their requisition for INR blood tests at their laboratory (N=6), informing us of upcoming surgery (N=4), and dropping out of the study (N=2). Lastly, one patient requested to be contacted by someone from the Clinic because they believed that *CallAssureCDM* gave them an incorrect dosing schedule. Shortly before the patient was contacted by *CallAssureCDM*, a clerk at the Clinic called the patient to give them their medication instructions (the clerk was unaware that the patient was enrolled in the *CallAssure* study). *CallAssureCDM*'s dosage schedule and the clerk's dosage schedule were different. After speaking with the patient and reviewing their record in *DawnAC*, it was determined that the clerk had given the patient the incorrect dosage schedule.

A total of 850 messages were documented as being successfully recorded on patients' answering machines. Of those messages, patients reported not receiving 27. It is possible that patients' family members erased the messages without informing the patient. Due to the less than perfect accuracy of the AMD algorithms, a number of problems related to messages recorded on answering machines occurred.

5.4.2.1.2 Subgroup analysis

Based on the Poisson regression model, patient age did not significantly predict the effectiveness of the IVRS (p=0.55). However, there was a trend toward decreased effectiveness of the IVRS as patient age increased.

5.4.2.1.3 Utility of the 'Reminder' and 'Missed' messages

Although the 'Reminder' and 'Missed' messages do not influence the workflow of Clinic staff, the proportions of each of these messages that were successfully delivered are of interest.

During the post-intervention period, 1,394 'Reminder' messages were scheduled to be delivered (Exhibit 9.10). Fewer 'Reminder' messages than 'Dosage' messages were scheduled because patients did not receive a reminder before their first INR test of the post-intervention period. After all contact attempts, 89% of the 'Reminder' messages were successfully delivered. As with the 'Dosage' message, the overall proportion of successfully delivered 'Reminder' messages increased after the 2nd and 3rd contact attempts. Sixty two percent and 38 % of successfully delivered messages were left on patients' answering machine and delivered to a person, respectively. These proportions are similar to those for the 'Dosage' message.

During the post-intervention period, 421 'Missed' messages were scheduled to be delivered (Exhibit 9.11). This number is greater than the total number of missed appointments because the 'Missed' message was programmed to call patients on Tuesdays, Thursdays, and Sundays until the Clinic received they INR result. Overall, 85.0% of the 'Missed' messages were successfully delivered. The majority of successfully delivered messages (69.1%) were left on patients' answering machines. It is noteworthy that 19% of the 1st contact attempts that reached a person failed. This is likely the result of patients receiving the call and hanging up after being told that they missed an appointment when they did not. As mentioned in the Patient satisfaction section (section 5.4.1.3), improvements to the dialogue many improve the success rate of this message.

5.4.2.2 Time required to monitor *CallAssureCDM*

It took 1 hour and 35 minutes per week to monitor *CallAssureCDM* (Exhibit 9.12). Approximately a third of this time was dedicated to reviewing the 'Report' and determining if patients requested to speak with someone from the Clinic or indicated that they started new medications. The other hour of monitoring time was dedicated to contacting patients, relaying patient information to the pharmacist, and receiving calls from patients.

A mean of 41 'Dosage' messages (Range 14-61) were scheduled to be delivered per week. On average, 4 messages were unsuccessfully delivered per week, 2 patients requested to be contacted

or indicated that they started new medications per week, and 1 patient did not receive a "successfully" delivered message per week.

As mentioned in the Overall utility of *CallAssureCDM* section (section 5.4.2.1), 1,557 'Dosage' messages were scheduled to be delivered during the post-intervention period. With the help of the clerk at the Clinic, it is estimated the time that it would take staff to make these calls. For 4 different time periods in 1 week, the clerk recorded the exact time it took to successfully deliver medication and appointment information to 20 patients. The clerk included the time it took to identify patients to be called and retrieve their information from *DawnAC*. The time it takes staff to successfully deliver 1 message was determined by dividing the total time for the week by the associated number of messages delivered (i.e. 80 messages). On average, it takes 2 minutes and 50 seconds to deliver 1 message. Therefore, it would have taken staff approximately 73.5 hours or 2 hours and 20 minutes per week to deliver the 1,557 messages. The best estimate is that *CallAssureCDM* reduces the workload of Clinic staff by approximately 1 hour per week.

5.4.3 Structure indicators

5.4.3.1 Comparison of study population with Clinic population

The study population was representative of the Clinic population (Exhibit 9.4). The proportion of females in the study and the median age of study patients were nearly identical to these measures for the Clinic population. There were no significant differences between the study population and the Clinic population with respect to the indications for OAC use or the target ranges. Compared to the Clinic population, the study population included fewer patients who took OACs for less than 1 year and more patients who took OACs for longer than 5 years. This difference is likely the result of the eligibility criterion that patients had to have completed 3 months of OAC therapy.

5.4.3.2 Resources required and technical problems during the study

It has already been emphasized that *CallAssureCDM* is not a stand alone application since it must be monitored by staff at a hospital or clinic. If a Clinic decided to purchase *CallAssureCDM*, an

employee must be taught how to monitor *CallAssureCDM* as well as be in regular contact with proprietary staff for IVRS support.

Despite Vocantas Inc.'s diligent support, 3 technical problems occurred throughout the post-intervention period. At the beginning of this period, calls were being recorded twice in the 'Report'. In other words, 2 rows of the 'Report' represented the same call. One of those calls was missing the patient identifier. Although Vocantas Inc. technicians installed a patch for this problem, it occurred an additional two times before the end of the study. Secondly, there were problems with the 'Primary' and 'Secondary' servers. On a number of occasions, the 'Primary' lost connectivity with *DawnAC* and shutdown. Unfortunately, the 'Secondary' server did not become operational as it is programmed to do. When this happened, I contacted Vocantas Inc. technicians immediately and they restarted the 'Primary' server. The third technical problem was associated with the 'WatchDog' notifications. During the end of the study, the 'WatchDog' server was sporadically sending Vocantas Inc. technicians notifications that the 'Primary' server was not operational. Upon investigation, the technicians concluded that the notifications were erroneous. On December 18, 2007, the technicians installed a fix that resolved the problems with the 'Report', the 'Primary' and 'Secondary' servers, and the 'WatchDog' server.

6.0 DISCUSSION

An interactive voice response system for oral anticoagulant (OAC) management was designed, implemented, and evaluated. The design and implementation phase lasted over a year. The evaluation phase took place over 8 months, during which a range of quantitative and qualitative indicators were recorded to evaluate the technology. Anticoagulation control while being monitored by the IVRS was noninferior to anticoagulation control achieved with traditional monitoring methods prior to the implementation of the IVRS (Section 5.4.1.1). The IVRS was well-received by a significant majority of patients (Section 5.4.1.3). The IVRS was also useful for communicating information to patients since approximately three-quarters of all 'Dosage' calls were successfully delivered and did not require further input from Clinic staff (Section 5.4.2.1). Lastly, the IVRS resulted in a minor reduction in the workload of staff (Section 5.4.2.2). Despite these promising results, an IVRS for OAC management is expensive to both purchase and maintain. It also requires diligent, ongoing supervision. Health care institutions must evaluate the costs and benefits of implementing such a technology prior to proceeding on such a course.

6.1 Effect of IVRS on anticoagulation control

An IVRS can be paired with a computerized decision support system (CDSS), such as *DawnAC*, to further improve the logistics of anticoagulation management. This combination resulted in timely delivery of patient medication information without deleterious effects on their anticoagulation control.

Patients in the study had excellent anticoagulation control prior to the study. A systematic review by Garg *et al.*[19] examined anticoagulation control of patients enrolled in studies that used a CDSS, similar to the one used in the study. Unlike the study patient population, none of the studies identified in Garg *et al.*'s review[19] reported a measure of anticoagulation control greater than 80%. In addition, only 2 studies[89,90] from a systematic review[11] of 67 studies that reported anticoagulation control included a patient group that spent greater than 80% of the time in therapeutic range.

6.2 Patient acceptance of IVRS

Similar to results from other studies[47,49,53] that used information technology to communicate with OAC patients, the majority of patients in the study were satisfied with the IVRS. Patients were very interested in the study and extremely willing to discuss their experience with the IVRS during the post-study interview. The selection of patients in favor of an IVRS for OAC management may have biased the results. However, the vast majority of patients approached for participation consented to enroll in the study. Overall, patients liked the IVRS because it provided them with the essential OAC dosing information. The most common complaint about the IVRS was that the dialogue was unclear or confusing. This issue can be resolved with further refinement and testing of the automated dialogues.

It was interesting that a third of patients continued with the IVRS because they felt that it would help the staff at the Thrombosis Clinic. During the post-study interview, the majority of patients praised the staff for delivering excellent care. These patients believed that the IVRS would decrease the workload of Clinic staff and, therefore, chose to continue to use it.

6.3 Study strengths

This study has several strengths. These strengths were identified by critically appraising the study using a guideline for evaluating prognostic studies by van Walraven and Hebert.[91] The first criterion of this guideline states that a study must include an 'inception cohort'. This means that study patients, selected using a clinically relevant and transparent eligibility criteria, must have similar histories with respect to the disease of interest. This criterion is important because studies with inception cohorts are more likely to yield valid, reliable results. The study satisfies this criterion. The inception cohort was very well defined and the eligibility criteria was reproducible (Section 4.3). Specifically, all study participants had stable anticoagulation control prior to enrollment. It is also noteworthy that a high proportion of patients approached for participation actually enrolled in the study. This lends to the generalizability of the results.

The second criterion of the guideline for evaluating prognostic studies states that patient follow-up must be both complete and long enough. This criterion is important because patients who are lost-to-follow-up may bias study results. Also, study outcomes may take extended periods of time to occur. The study meets this second criterion of the evaluation guideline. This study had perfect patient follow-up of a relatively large patient population. hat this is the primary strength of this study. All patients completed the post-study interview and provided feedback on the IVRS. Feedback was even collected from patients who were removed from the study and were no longer taking warfarin. Also, the majority of the patients completed the 3-month study. Lastly, patients were followed for an adequate length of time (mean of 4.2 months) to obtain an accurate estimate of their level of anticoagulation control.

The third criterion of the guideline for evaluating prognostic studies states that outcomes must be blind (when applicable) and objective. This is important because outcomes that are subject to bias are more likely to yield invalid results.[91] The study meets this criterion of the evaluation guideline. The primary outcome, anticoagulation control, was objective, clinically important, and clearly defined. The secondary outcomes were also clearly defined (Section 4.9). In addition, a single person conducted all post-study interviews to ensure a consistent wording and sequence of the interview topics.[92] The combination of relevant indicators provide a more comprehensive and less-biased assessment of the IVRS, especially since the study had perfect patient follow-up. The range of indicators also ensures a complete assessment of the intervention's effect on patients and the health care team.

Based on van Walraven and Hebert's guideline for evaluating prognostic studies[91], the study meets the criteria of a high quality study.

6.4 Study limitations

The limitations of the study must be noted. The primary limitation of the study involves the study population. The patients included in the study were a very select group of OAC users. The majority of patients monitored by the Clinic have very stable anticoagulation control. Therefore,

these patients are not truly representative of most community-based patients taking OAC. Anticoagulation control for community based studies included in the systematic review[11] of 67 studies ranged from 34% to 77%. This is not to say that an IVRS could not be used to monitor patients with unstable anticoagulation control. In fact, the 'Reminder' and 'Missed' messages may be especially helpful in this patient group to improve medication and appointment adherence.

Also, most patients at the Clinic are notably compliant with their medication use and INR appointments. Occasionally, patients who are unable to follow the Clinic's recommended dosage schedule or miss many INR appointments are sent to their family physician for OAC management. It must also be emphasized that patients volunteered to participate in the study. Patients who had some trepidation of new technology or are uncomfortable participating in a research study declined to participate. However, two-thirds of the patients approached for study enrollment participated in the study. It is uncertain if patients would be satisfied with the IVRS if they were forced, rather than volunteered, to use it.

The second limitation of the study is the pretest-posttest design. The primary weakness of this design is the lack of a concurrent comparator. Without a concurrent comparator, it is difficult to conclude that the difference in outcomes between the pre and post-intervention periods is solely due to the IVRS. It is possible that changes in the post-intervention period could be a function of unmeasured and extraneous factors (e.g. new staff at the Clinic). If future quasi-experimental studies are conducted in this area, alternative study designs using a concurrent control group or multiple pretest-posttest periods should be considered. Alternatively, a truly randomized design could be used.

The third limitation of the study is that an accurate measure of the proportion of missed appointments in the pre-intervention period could not be obtained due to the biased *DawnAC* data. Therefore, definitive conclusions on the effectiveness of the 'Reminder' message can not made.

The fourth limitation of the study is that technical problems with the IVRS could have adversely affected the study. As mentioned in the Notification to contact patients section (section

4.5.11.3), the email that alerted staff to contact patients did not work for a short period of time. During this time, a number of patients who requested a contact from clinic staff received none as a result of the problem with the email notification. Another technical problem that affected a number of patients was the periodic shutdowns of the 'Primary' server (Section 5.4.3.2). This problem delayed the delivery of patient information. These technical problems may have resulted in biased patient satisfaction outcomes.

The final limitation deals with the surrogate nature of the primary outcome. A recent study demonstrated that anticoagulation control is – using traditional statistical criteria - an invalid surrogate outcome for hemorrhagic and thromboembolic events in most situations.[93] The authors developed a model, using Monte Carlo simulation techniques, that translated changes in anticoagulation control (the surrogate outcome) to changes in hemorrhagic and thromboembolic event rates (the clinical outcome). The authors identified all RCTs in which anticoagulation control was the primary outcome. Seven RCTs reported a significant improvement in anticoagulation control for the intervention group. However, these improvements never resulted in a significant decrease in hemorrhagic and thromboembolic events. Further analyses showed that very large changes in anticoagulation control were required to demonstrate significant changes in the clinical outcomes. A longer study that included a greater number of patients and measured clinical outcomes as the primary outcome would better allow researchers to evaluate the clinical effectiveness of the IVRS.

Despite the comprehensive evaluation of the IVRS, future studies using a randomized design are required to determine the true utility of IVRS for anticoagulation control. Future studies should aim to include a more representative sample of OAC users. For example, new OAC users and patients with unstable anticoagulation control may be included. However, it must be noted that these studies will be limited to patients monitored by anticoagulation clinics that use *DawnAC*, or a similar type of application. This is because the IVRS must be integrated with a computerized decision support system for OAC management.

If future IVRS studies are planned, health care institutions using the technology need to realize that the calling system must be monitored closely. They must also ensure that the technology company providing the IVRS will be available to provide support. This is important since technical problems may result in untimely communication of patient information. Lastly, health care institutions should expect an increase in the time required to monitor the system as the number of patients using the IVRS increases. Specifically, the time required to contact patients, relay patient information to the pharmacist, and receive calls from patients will increase as the number of patients enrolled in the system increases.

6.5 The study in context of other IVRS studies

I conducted a literature review to compare the IVRS study with those that have been published. I identified 83 articles, published between 1989 and 2007, that examined the effect of an IVRS intervention on patient and/or process outcomes. A number of these articles reported on different subgroups within the same study. Therefore, the 83 articles detailed different aspects of a total of 75 individual studies. Among these studies, approximately a third had a quasi-experimental design and the median sample size was 218. With respect to these characteristics, the study is similar to published IVRS studies.

The most striking and important difference between this study and published IVRS studies is the range of outcomes measured. This IVRS evaluation consisted of 9 indicators that examined clinical, process, and structure outcomes. Only 4 published studies[94-97] conducted a similar comprehensive assessment of an IVRS. The majority of studies failed to provide a comprehensive assessment for 2 main reasons. First, few published studies measured clinical outcomes. Of the 75 studies identified, only 14 measured clinical outcomes (e.g. HbA1c levels). Most studies examined the effect of the IVRS on changes in participants' behavior, such as physical activity and medication adherence. Second, very few studies described how the IVRS fit within the existing organization of health services. I identified only 12 studies that described the resources required to implement and

maintain the IVRS. In summary, the assessment of IVRS in the study was more comprehensive than most published IVRS studies.

6.6 Recommendations for future use of an IVRS in OAC management

There is a role for an IVRS in anticoagulation management. However, this technology must be optimized before healthcare organizations invest in it and implement it on a larger scale. Based on this experience, I recommend that a number of changes be made to improve an IVRS for OAC management. First, the automated dialogues must be carefully designed and periodically refined. Healthcare institutions should collect and review patient feedback on the IVRS dialogues. Simple dialogues are essential for the effectiveness of an IVRS. Second, an IVRS should be programmed to re-attempt 'failed' calls after a couple of hours have passed. The set-up of *CallAssureCDM* was inefficient since it re-attempted 'failed' calls within minutes of the initial call. Finally, an IVRS should allow users to select the telephone number that will be used to contact patients. Approximately 10% of patients in the study requested to be contacted at work or at a cellular phone. Unfortunately, *CallAssureCDM* was designed to contact patients using the home phone number. This option would improve staff usability of the IVRS.

Given these recommended changes, additional assessment of an IVRS for OAC management is required. As mentioned in the study limitations section (section 6.4), a randomized controlled trial that includes a more representative patient population should be considered. Institutions that plan to conduct future studies or utilize an IVRS should designate a project team. This team, which includes a representative from the various parties, should attend regular meetings to ensure that all parties are up-to-date on both the study progress and study problems.

Implementing health information technology is challenging. It requires cooperation between the technology company and the health care institution. Dedicated and adaptive staff members from both parties are essential to designing, implementing, and evaluating health information technology. In this study, I have highlighted the various parties required to design and implement an IVRS for OAC management. I have also demonstrated that an IVRS is useful in communicating medication

and appointment information to OAC patients monitored by an anticoagulation clinic. Further use and refinement of IVRSs for OAC management will continue to improve their utility.

7.0 CONCLUSION

An IVRS was a feasible and effective method of communicating medication information in this population of OAC patients. Future work is required to determine the generalizability of these results.

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9.0 EXHIBITS

Exhibit 9.1 Framework of anticoagulation management

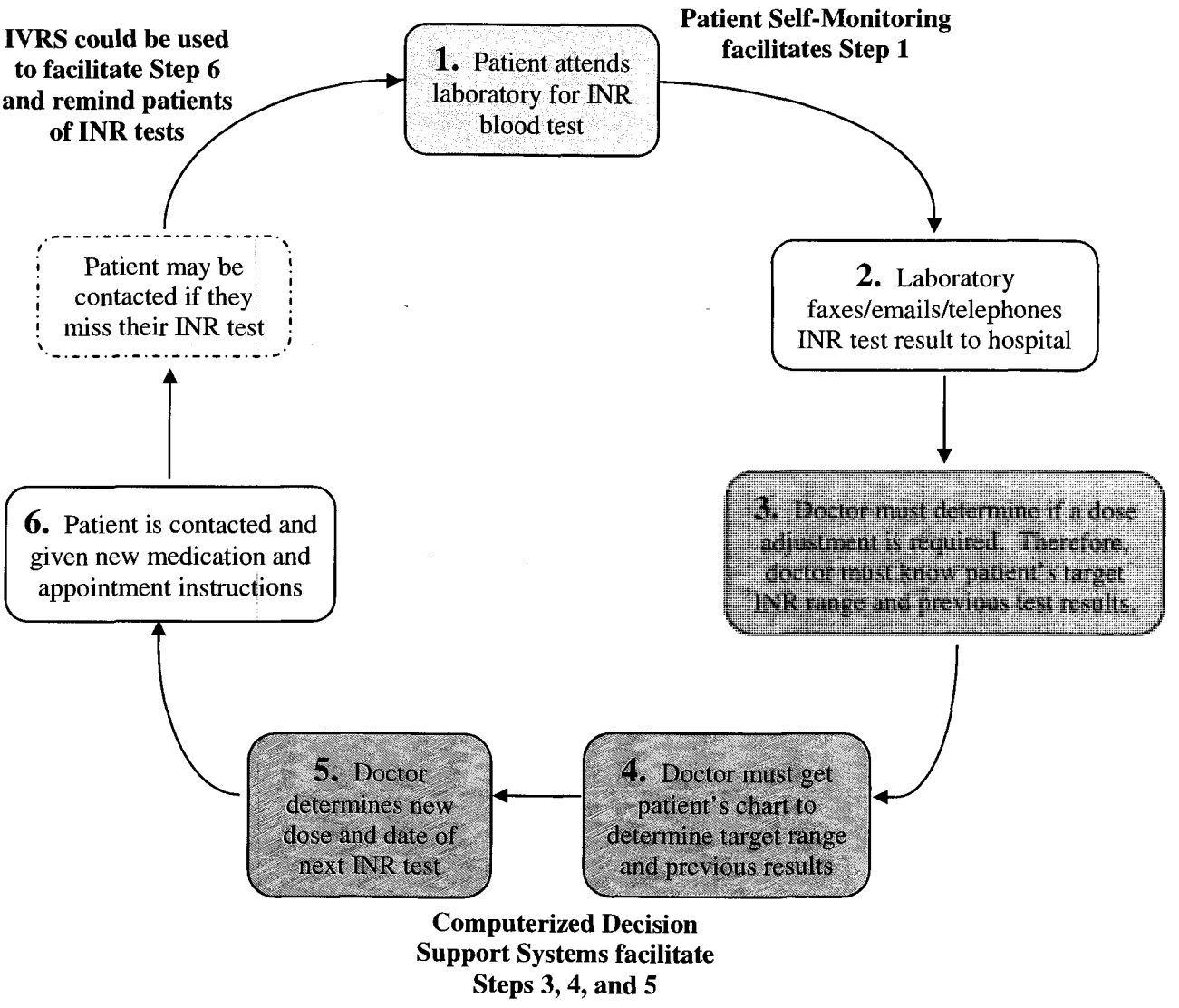
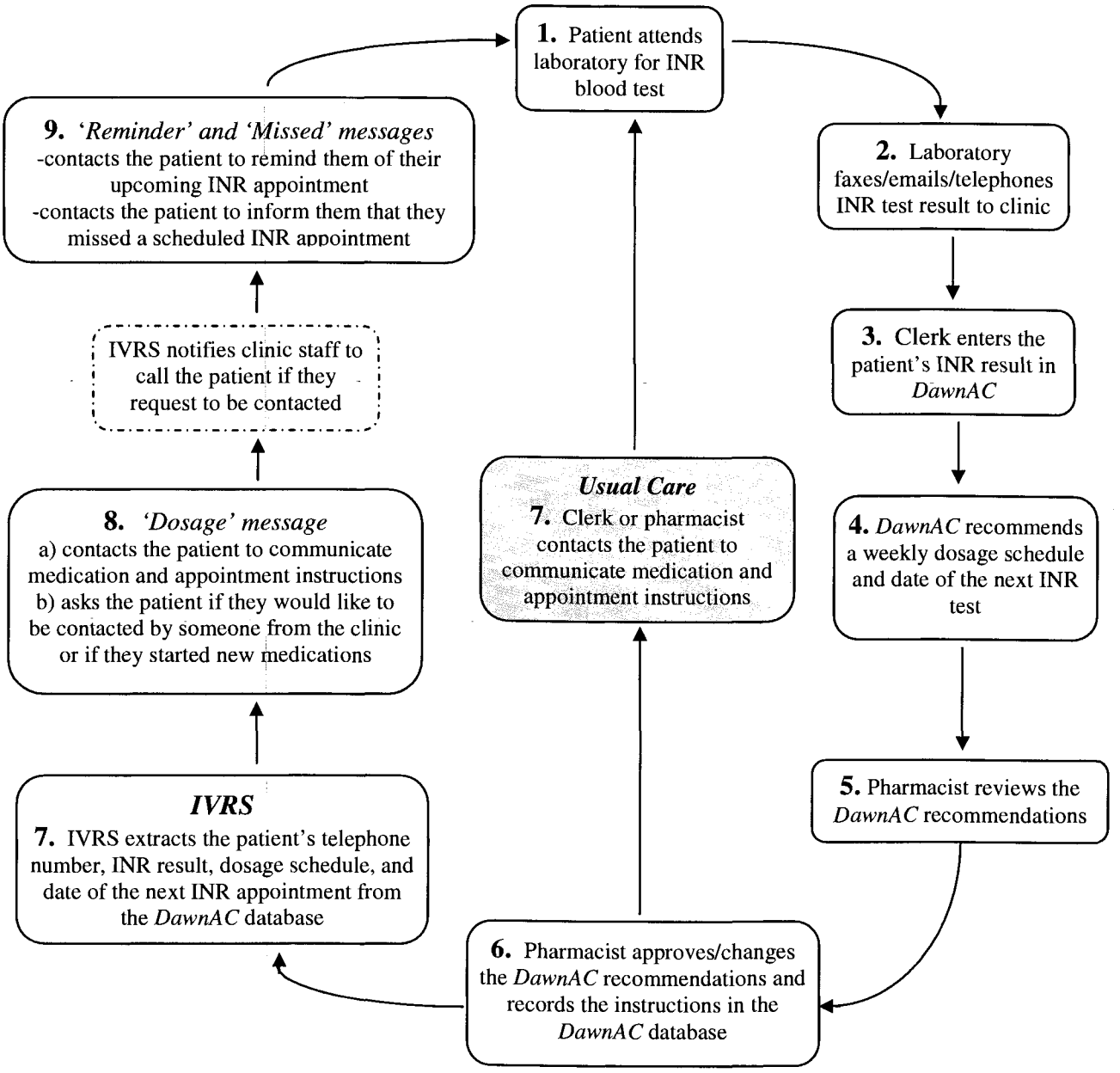
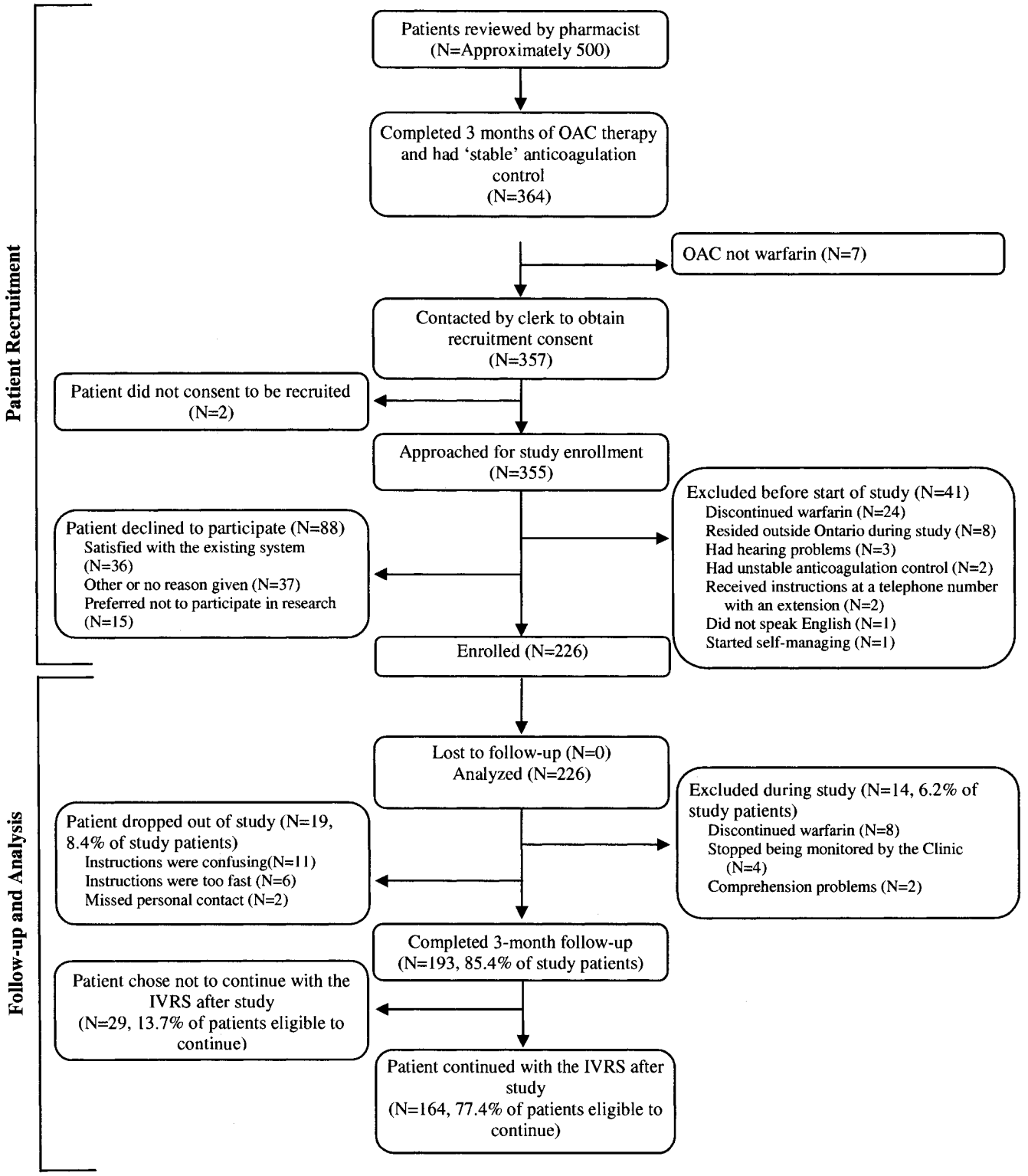


Exhibit 9.2 Schedule of events for IVRS and usual care patients



White boxes represent the standard monitoring framework at the Thrombosis Clinic for both interactive voice response system (IVRS) patients and usual care patients. Yellow boxes represent the interactive voice response system (IVRS) intervention and the green box represents usual care only.

Exhibit 9.3 Flow diagram of patient recruitment, follow-up, and analysis



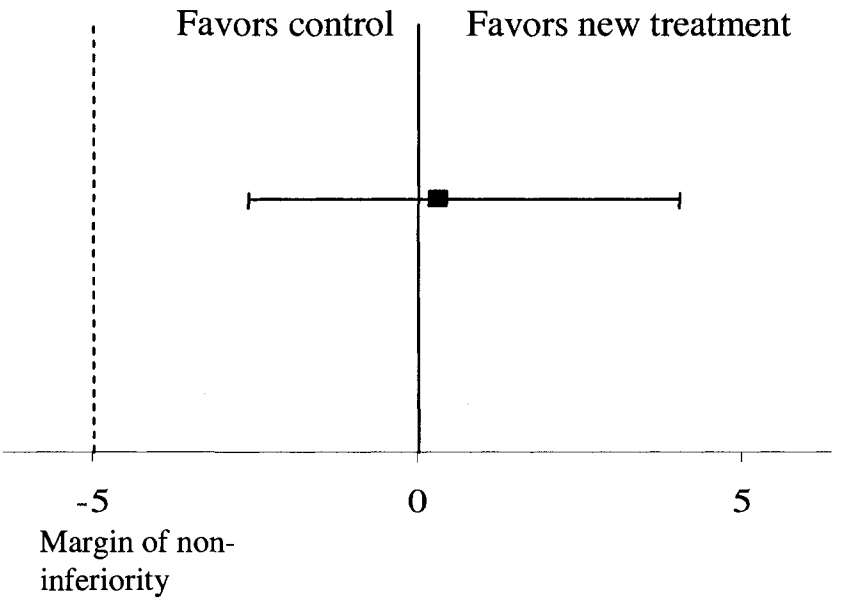
OAC = oral anticoagulant; IVRS = interactive voice response system

Exhibit 9.4 Characteristics of Thrombosis Clinic patients stratified by study participation

Characteristic	Study population	Rest of Clinic population *
N	226	913
Female (%)	107 (47.4)	432 (47.3)
Median age in years (Interquartile range)	58 (48-68)	60 (49-73)
Indication for OAC use (%)		
Venous thromboembolism	179 (79.2)	769 (84.2)
Atrial fibrillation	7 (3.1)	38 (4.2)
Mechanical heart valve	5 (2.2)	22 (2.4)
Other	35 (15.5)	84 (9.2)
Target INR range (%)		
2.0 - 3.0	209 (92.5)	866 (94.9)
2.5 - 3.5	9 (4.0)	34 (3.7)
1.5 - 2.5	6 (2.7)	12 (1.3)
3.0 - 4.0	2 (0.9)	1 (0.1)
Duration of OAC use in years (%)		
< 1	45 (19.9)	296 (32.4)
1-5	110 (48.7)	434 (47.5)
> 5	71 (31.4)	183 (20.1)
Mean follow-up in months (SD)	4.2 (1.8)	
Total observation time in months	942.2	

* Includes non-study patients who had completed the initiation phase of OAC therapy and were monitored at the Ottawa Hospital Thrombosis Clinic on December 4, 2007.
OAC = oral anticoagulant

Exhibit 9.5 Non-inferiority test for anticoagulation control



The mean difference in anticoagulation control between the 2 study periods is 0.36%. The confidence interval for this estimate (-2.95 – 3.67) includes zero. Therefore, anticoagulation control during the intervention period was non-inferior to patients' anticoagulation control during the pre-intervention period.

Exhibit 9.6 Patients' satisfaction with the IVRS

	N	%
Completed the 3-month follow-up	**193**	**85.4***
Patient continued with the IVRS after the study	**164**	**77.4**
Received clear, timely information	86	40.6
Easier on Clinic staff	53	25.0
Received clear information and had the option to speak with Clinic staff	22	10.4
Appreciated receiving the 'Reminder' message	3	0.1
Patient chose not to continue with the IVRS after the study	**29**	**13.7**
Missed personal contact	12	5.7
Instructions were confusing	7	3.3
Instructions were too fast	5	2.4
Recognitions problems with answering machine	5	2.4

* Percentage based on 226 patients. All other percentages are based on 212 patients (the number of patients eligible to continue with the interactive voice response system (IVRS).)

Exhibit 9.7 Summary of patient impressions regarding the IVRS

	'Dosage' message		'Reminder' message *		'Missed' message **	
	Comment	N (% of 226)	Comment	N (% of 216)	Comment	N (% of 98)
Message Clarity	-Instructions were easy to understand	165 (73.0)	-Instructions were easy to understand	206 (95.4)	-Instructions were easy to understand	66 (67.3)
	-Instructions should be slower	45 (19.9)	-Instructions should be slower	10 (4.6)	-Instructions were confusing (Patient received this message on the same day they attended their INR appointment)	32 (32.7)
	-The dosage schedule was confusing	16 (7.1)				
Ease of interacting with the automated dialogue	-Responding 'Yes' or 'No' to the automated dialogue was straightforward	179 (79.2)	-Responding 'Yes' or 'No' to the automated dialogue was straightforward	203 (94.0)	-Responding 'Yes' or 'No' to the automated dialogue was straightforward	59 (60.2)
	-Question 1 ("Are you a patient or the caregiver of a patient?") was confusing	24(10.6)	-Patient responses were not recognized by the IVRS	13 (6.0)	-Patient responses were not recognized by the IVRS	39 (39.8)
	-Patient responses were not recognized by the IVRS	23 (10.2)				
Message Usefulness	-Patient was satisfied receiving their instructions from *CallAssureCDM*†	174 (77.0)	-Helpful in keeping appointments	166 (76.9)	-Helpful in attending missed appointments	47 (48.0)
	-Patient would prefer to receive their instructions from Clinic staff†	52 (23.0)	-Patient was diligent with appointments and felt that this message was unnecessary	50 (23.1)	-Patient found the message annoying since they missed the appointment for a reason (not because they forgot about it)	61 (52.0)

† Includes patients who were removed from the study.
* Percentages are based on 216 patients. 4 patients requested not to receive the message and 6 patients withdrew or were removed from the study before receiving the message.
** Percentages are based on 98 patients. 124 patients did not miss an appointment and 4 patients requested not to receive the message.
IVRS = interactive voice response system

Exhibit 9.8 Overall utility of the IVRS

	N	% of total
'Dosage' messages scheduled to be delivered	**1557**	**100.0**
Successfully delivered and required no additional input from Clinic staff	**1211**	**77.8**
Input from Clinic staff was required	**346**	**22.2**
Patient had an excessively low or high INR result*	143	9.2
Message was unsuccessfully delivered	128	8.2
Patient requested to be contacted by someone from the Clinic	48	3.1
Message was recorded as being successfully delivered, but the patient called the clinic because they did not receive the message	27	1.7

Includes 'Dosage' messages delivered between May 7, 2007 and December 14, 2007.
* These patients were called by Clinic staff to identify factors that may be responsible for the non-therapeutic INR.

Exhibit 9.9 Proportion of successfully delivered 'Dosage' messages after all attempts

	After all attempts		Contact attempt					
			1		2		3	
	N	% of total	N	% of total	N	% of total	N	% of total
'Dosage' messages scheduled to be delivered	1557	100.0	1557	100.00	388	24.9	197	12.7
Successfully delivered	1429	91.8	1169	75.1	191	12.3	69	4.4
To answering machine	850	54.6	714	45.9	103	6.6	33	2.1
To patient or caregiver	579	37.2	455	29.2	88	5.7	36	2.3
Unsuccessfully delivered	128	8.2	388	24.9	197	12.7	128	8.2
To patient or caregiver	58	3.7	235	15.1	109	7.0	58	3.7
Busy/No Answer/Other	70	4.5	153	9.8	88	5.7	70	4.5

This table details the calling outcomes after multiple attempts to contact patients.

Exhibit 9.10 Proportion of successfully delivered 'Reminder' messages after all attempts

	After all attempts		Contact attempt					
			1		2		3	
	N	% of total	N	% of total	N	% of total	N	% of total
'Reminder' messages scheduled to be delivered	1394	100.0	1394	100.0	328	23.5	199	14.3
Successfully delivered	1240	89.0	1066	76.5	129	9.3	45	3.2
To answering machine	775	55.6	681	48.9	64	4.6	30	2.2
To patient or caregiver	465	33.4	385	27.6	65	4.7	15	1.1
Unsuccessfully delivered	154	11.0	328	23.5	199	14.3	154	11.0
To patient or caregiver	74	5.4	189	13.6	106	7.6	74	5.4
Busy/No Answer/Other	80	5.7	139	9.9	93	6.7	80	5.7

This table details the calling outcomes after multiple attempts to contact patients.

Exhibit 9.11 Proportion of successfully delivered 'Missed' messages after all attempts

	After all attempts		Contact attempt					
			1		2		3	
	N	% of total	N	% of total	N	% of total	N	% of total
'Missed' messages scheduled to be delivered	421	100.00	421	100.0	125	29.7	77	18.3
Successfully delivered	356	84.6	296	70.3	48	11.4	12	2.9
To answering machine	246	69.1	211	50.1	26	6.2	9	2.1
To patient or caregiver	110	30.9	85	20.2	22	5.2	3	0.7
Unsuccessfully delivered	65	15.4	125	29.7	77	18.3	65	15.4
To patient or caregiver	16	3.8	79	18.8	34	8.1	16	3.8
Busy/No Answer/Other	49	11.6	46	10.9	43	10.2	49	11.6

This table details the calling outcomes after multiple attempts to contact patient

Exhibit 9.12 Time required to monitor the IVRS for 226 patients

Monitoring task	Additional description	Patient contact required	Minutes per week
Review the 'Report'	This task is performed at least once daily to identify patients whose 'Dosage' messages were unsuccessfully delivered.	-	25
Contact patients whose 'Dosage' messages were unsuccessfully delivered	The clerk must consult *DawnAC* for the patient's telephone number and medication instructions. It takes approximately 5 minutes to consult *DawnAC* and contact the patient.	'Dosage' messages were unsuccessfully delivered to a mean of 4 patients per week	20
Check email for notification of patients who requested to speak with someone from the Clinic or indicated that they started new medications	This task is performed at least once daily. The clerk should also review the 'Requests' section in the web-based interface to ensure that the email notification is working properly.	-	10
Contact patients identified from the previous task	Once again, the clerk must consult *DawnAC* for the patient's telephone number.	A mean of 2 patients per week were contacted	10
Correspond with the pharmacist at the Clinic	This includes notifying the pharmacist to contact patients who requested to be contacted or indicated that they started new medications and passing on patient information (e.g. updating address or changing the next INR appointment).	-	25
Receive calls from patients	On occasion, messages are recorded as being successfully delivered, but the patient did not receive the message. In this case, the patient calls the Clinic to collect their medication and appointment instructions.	A mean of 1 patient per week did not receive a "successfully" delivered message	5
Total time required to monitor the IVRS			**95**

The 226 patients had a mean of 41 INRs per week.

10.0 Appendix

The Ottawa Hospital | L'Hôpital d'Ottawa

Research Ethics Board
Conseil d'éthique en recherches
798-5555 ext 14146, 14902 or 15072
Fax No. ~ 761-4311
http://www.ohri.ca/ohreb/

Thursday, July 27, 2006

Dr. Carl Van Walraven
Ottawa Hospital - Civic Campus
Clinical Epidemiology Unit
Ottawa Health Research Institute
1053 Carling Avenue, Rm C-405
K1Y 4E9

Dear Dr. Van Walraven:

Re: Protocol # 2006500-01H **Improving Communication to Oral Anticoagulant Patients Using an Interactive Voice Response System: A Pilot Prospective Cohort Study**

Protocol approval valid until - Thursday, July 26, 2007

I am pleased to inform you that your study (listed above), Protocol received July 6, 2006, the English Patient Satisfaction Survey and Version 4 of the English Information Sheet and Consent Form received July 21, 2006 were given expedited review by the Ottawa Hospital Research Ethics Board (OHREB) and are approved. No changes, amendments or addenda may be made in the protocol without the OHREB review and approval.

The validation dated should be indicated on the bottom of all consent forms and information sheets (see copy attached). Approximately two months prior to the expiration date listed above, a single renewal form should be sent to the OHREB office.

The Tri-Council Policy Statement requires a greater involvement of the OHREB in studies over the course of their execution. The OHREB will review the new information to determine if the protocol should be modified, discontinued, or should continue as originally approved.

Yours sincerely. .

Raphael Saginur, M.D.
Chairman
Ottawa Hospital Research Ethics Board

/ip

11.0 ACKNOWLEDGEMENTS

Shemina Kherani is the pharmacist at the Clinic who was involved in the entire study. When 'the pharmacist' is mentioned in the Methods section, we are referring to her. I corresponded with Ms. Kherani on a daily basis to pass on patient information, ask questions about OAC therapy, or discuss the study. The study would not have been possible without her cooperation and patience.

Lesley Yeung is the clerk at the Clinic responsible for calling patients to deliver their medication information. She obtained verbal consent from the patients during the recruitment period. I corresponded with Ms. Yeung on a weekly basis to relay patient information. She was extremely accommodating and we would not have been able to recruit the patients without her help.

Geoff Lewis is another pharmacist at the Thrombosis Clinic. His main involvement in the study occurred during the implementation and testing phase. Mr. Lewis is the system administrator of *DawnAC* and occasionally replaced Ms. Kherani when she was out of the office.

Wayne Lowe and Rick Wayner are members of the O.H.R.I. technical support staff. We would not have been able to install the IVRS at the Clinic without their help. They also assisted Mr. Lewis in upgrading *DawnAC* version 7.1 to version 7.2.

Dr. Marc Rodger, the Head of the Thrombosis Program at the Ottawa Hospital, was critical in obtaining the necessary approvals to conduct the study. He also collaborated with Vocantas Inc. to develop the IVRS. Furthermore, he enlisted the help of his knowledgeable staff to participate in the study.

Lastly and most importantly, the study would not have been possible without the help of Dr. Carl van Walraven and Dr. Alan Forster. Dr. van Walraven was helpful in designing the study and provided consistent support throughout. Dr. Forster was instrumental in both developing the IVRS and implementing it at the Clinic. He coordinated all parties involved in the study. During the study, he provided guidance on the clinical, methodological, and business related aspects of the study.