CONFIDENTIAL

IMPACT-AF

Integrated Management Program Advancing Community Treatment of Atrial Fibrillation

Protocol #: IMPACT-AF-2013
Pharmaceutical Study Support: Bayer Inc.
Clinical Trials Identifier: NCT01927367
Principal Investigator: Dr. Jafna Cox
Version #: 4.2
Date of Protocol: September 26, 2017

Prepared by:
Dr. Jafna Cox, Dr. Raza Abidi, Dr. Samina Abidi, Dr. Ratika Parkash; and, Dr. Feng Xie, McMaster University and Dr. Lehana Thabane, Population Health Research Institute, Hamilton Health Sciences, Ontario; with review by Dr. Jim MacKillop, CBDHA.
c/o Dr. Jafna Cox
Queen Elizabeth II Health Sciences Centre
New Halifax Infirmary Site, Room 2147
1796 Summer Street
Halifax, Nova Scotia, Canada
B3H 3A7
Tel. 902-473-7811
Fax. 902-473-8616
jafna.cox@nshealth.ca

This document contains information which is of a confidential nature. It is not to be disclosed to any other person or party without the written approval of Dr. Jafna Cox.

IMPACT-AF

Integrated Management Program Advancing Community Treatment of Atrial Fibrillation

ABSTRACT: Atrial fibrillation (AF) is the most common abnormality of cardiac rhythm. It is also a disease of aging, affecting 3% of adults aged ≥ 45 years- and- 12% of those aged ≥ 75. Individually, AF's rapid and irregular heart beat is most frequently perceived as undesirable palpitations, but more threatening impacts are heart failure, catastrophic stroke and premature death. At the public health level, the burden of managing AF is driven by our rapidly aging population and bears an annual cost of $5000 per patient.

Optimal care of AF patients is also hindered by large gaps between usual care and best care. For example, a large proportion of AF patients at moderate to high risk for stroke do not receive guideline recommended thromboprophylaxis; and of those that do, many are not optimally controlled. The presence of these care gaps is particularly disappointing in light of recent therapeutic innovations such as more efficacious anti-coagulant drug therapies and evidence that an integrated multi-disciplinary approach to delivery of AF care facilitates improved care and outcomes, including large reductions in hospitalizations. Thus, opportunities to make things better are at hand.

We propose a patient-centered and community-focused management program (IMPACT-AF) to grasp these opportunities and determine if patients with AF can be managed as effectively (clinical outcomes) and more efficiently (economic outcomes) in primary care as they are in specialized care. The premise of IMPACT-AF is that primary care providers within the community when supported by an electronic AF patient management system that offers: a) clinical decision aids based on clinical guidelines for AF; and, b) a communication medium for data sharing and referrals, with the specialized AF management centre in Halifax, will lead to improved diagnosis and standardized disease management, including increased use of proven therapies for AF rhythm and rate management, and better stroke prevention. We expect - frequent measurement and feedback of actual care practices, patient outcomes and other relevant disease / health information, to drive positive behaviour in both practitioners and patients. The overall result will be cost-efficient improvement of care and outcomes for AF patients.

The primary outcome is a decrease in CV hospitalizations, with secondary outcomes of clinical, process of care and economic relevance. The cluster-randomized study design will permit measurement and comparison of the clinical decision support system pre and post intervention, and across cases. A principal assumption is that IMPACT-AF will build on the principles and practices of benchmark disease management projects like ICONS, particularly in aligning with provincial and regional health policies that direct support to primary care and data management resources that address public health burdens. We anticipate that IMPACT-AF will successfully extend a more clinically effective, cost-efficient and sustainable social-networking model of health management to a segment of our aging population who need things to be better. In doing so, IMPACT-AF will also produce, markedly improved stakeholder outcomes and satisfaction – all of which can be modeled in other areas of health care priority.

Table of Contents

List of Abbreviations

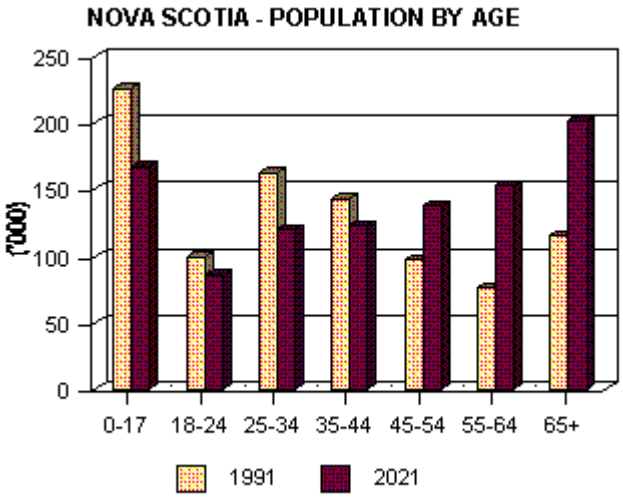
AF: Atrial Fibrillation
CDSS: Clinical Decision Support System
IT: Information Technology
FPN: Family Practice Nurse
NP: Nurse Practitioner
NS: Nova Scotia
PCP: Primary Care Provider
QEII HSC: Queen Elizabeth II Health Sciences Centre
RN: Registered Nurse

1.0 BACKGROUND AND RATIONALE

1.1 The Problem: Increasing Burden, Significant Risk and Care Gaps

Atrial fibrillation (AF) is the most common sustained cardiac rhythm abnormality. It affects 1-2% of the entire population [1, 2]; and, is age related. The incidence doubles with each decade beyond age 55, eventually afflicting 1 in 10 octogenarians [3, 4]. With the age distribution of the current Nova Scotian population (Figure 1), the prevalence of AF patients over 65 years is probably between 10,000 and 20,000 patients. As North American populations continue to age, the number of AF patients will likely rise between 2- and 3-fold in the near future [4, 5]. Overall, the lifetime risk is about 26% for males; and, 23% for females [1].

Figure 1. Comparative age distributions in the Nova Scotian population



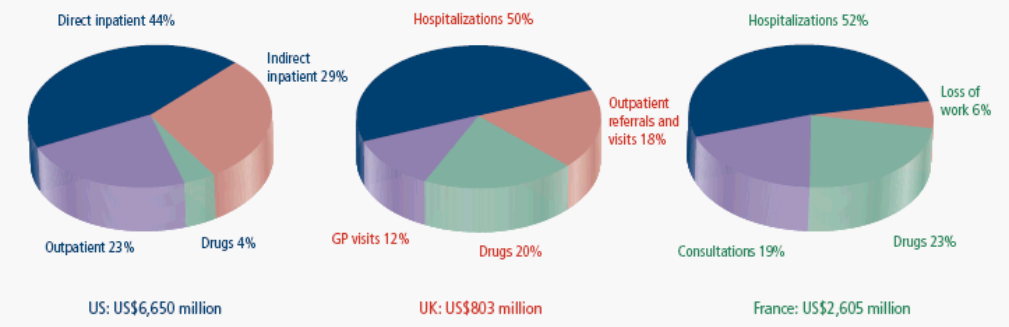
AF is linked with increased mortality, substantial morbidity and high costs [7, 8]. The Framingham and other epidemiology studies have found AF to be associated with a 1.5 to 1.9-fold risk of death even after adjustment for pre-existing cardiovascular conditions commonly associated with AF [9, 10]. AF is an important and independent risk factor for stroke, increasing the risk of such events by 5-fold [11-13]. Indeed, AF accounts for approximately 15-20% of all strokes [11-14]. Risk of stroke in AF patients increases with age, being around 2% in 50-59 year olds; and, increasing to about 24% in 80-89 year olds. Importantly, the strokes associated with AF are more likely to be fatal or very disabling than are strokes associated with other etiologies [15].

Apart from death and stroke, AF markedly impairs quality of life [16, 17]. AF is symptomatic in 39% patients with severity of symptoms may range from a 'nuisance' feeling of palpitations to debilitating symptoms that do not permit performance of activities of daily living, interfere with normal livelihood and significantly impair exercise tolerance [18]. The most severe symptoms are those resulting in hemodynamic compromise and heart failure, which are associated with poor prognosis and increased mortality. Approximately 1/3 of patients with AF present to the emergency room (ER) at some time due to symptoms and they represent 3-6% of all medical admissions to hospital [19-23]. The overall hospitalization rate for AF in Canada is approximately 583 per 100,000 of population [21]; and, in an as yet unpublished pilot study

conducted at the QEII Health Sciences Centre in Halifax, 92% of patients with persistent atrial fibrillation had undergone prior cardioversion and 90% had experienced more than one ER visit.

The annual cost of AF care to the Canadian health care system is estimated at $4840 per patient [24]. A recent study suggests that the costs associated with warfarin therapy, alone, may be as much as $1232-$2012 per patient, per year [25]. Care costs are distributed across outpatient encounters, ER visits, inpatient hospitalizations and drug therapies in roughly similar proportions in France and the United Kingdom, versus the United States where relatively more is spent on inpatient care (Figure 2) [26-28]. Overall, estimated care costs of hospitalized AF patients, compared to patients without AF, were 9 to 23 fold greater [29].

Figure 2. Total and distribution of health care spending on AF



While prevention of AF by controlling known risk factors is a long-standing and ever-increasing public-health target, the incidence and risk of AF are still increasing [30-36], despite advances in co-morbidity therapies, especially for hypertension and heart failure [37-54].

Traditionally, the major therapeutic interventions in AF patient care are directed at modifying or reversing the irregular rhythm and fast heart rate, as well as reducing the predisposition of the dysfunctional atria to form and expel clots that cause strokes. Anticoagulant therapy in AF is influenced by the need to balance the benefit of this therapy in terms of stroke prevention with its side effect of enhancing the risk of bleeding.

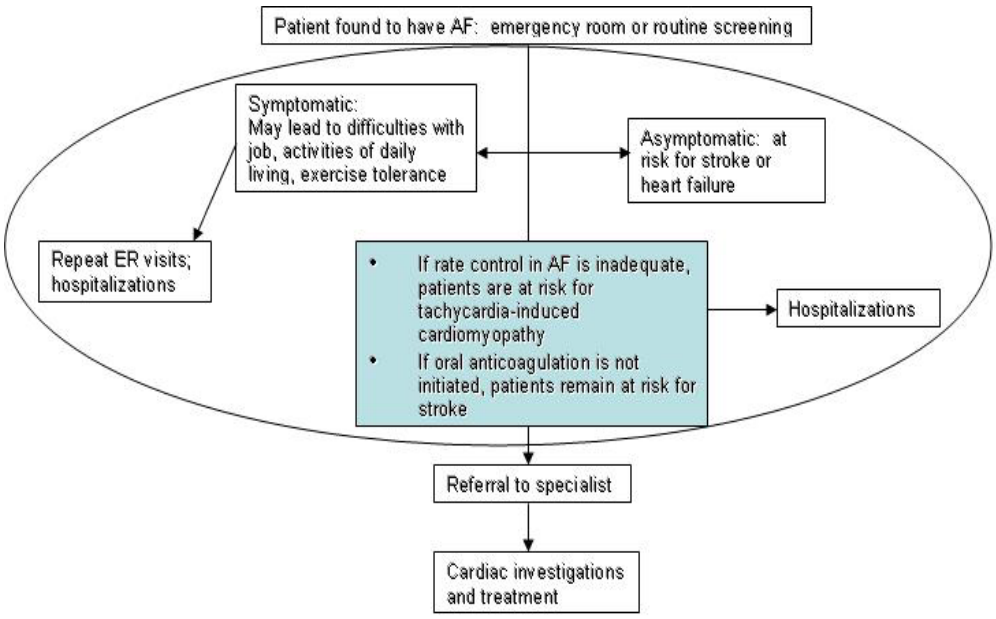
Most care is delivered by family physicians with eventual referral to specialists, although repeated ER visits and hospitalizations may occur prior to specialty assessment. Figure 3 illustrates recommended care steps for newly diagnosed patients [31]. Unfortunately, each referral step, whether for consultation, investigation or management, can be associated with its own wait time, or temporal care gap. This can result in an overall wait for definitive diagnosis and treatment that extends beyond the norms endorsed by the CCS Access to Care Working Group and the Canadian Heart Rhythm Society, both of which suggest that outpatient assessment and investigations should be no longer than 4 to 12 weeks, depending on patient urgency [55].

Although primary care settings are the first line of health care in the community, primary care providers (PCP) experience gaps in knowledge, skills and competencies with respect to best

evidence-based approaches concerning the management of complex chronic diseases, such as AF even though guidelines and best practice resources are freely available [56, 57]. Patients themselves have difficulty understanding their condition, treatment options and how to self-manage their AF. Despite the availability of evidence-based clinical guidelines, protocols and pathways, the reality is that such decision-support aids are often unavailable at the point-of-care to assist PCPs and patients in making evidence-based decisions regarding AF treatment and management. There is a fundamental need to translate published medical knowledge more quickly and practically into patient care. One way of doing so is through computerized decision support aids so that PCPs are better equipped with the clinical decision-making tools that will allow the best evidence-based, proactive and standardized care. Such support is expected to reduce both the clinical and financial burdens of common chronic diseases, including AF.

Several clinical trials comparing rate control to rhythm control as management for the rapid and irregular rhythm of AF have found no difference in mortality, rates of thromboembolism or bleeding between the two strategies [58]. Subsequent re-analysis of the largest of these trials, the Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) study, did, however, suggest a survival advantage in those who maintained sinus rhythm [59].

Figure 3. Recommended care flow for patient with newly-diagnosed AF



Unfortunately, for those patients with longstanding AF, and the elderly, who form the major part of the whole AF population, cardioversion to, and then maintenance in, sinus rhythm can be especially challenging [60]. The outcome benefit gained by attaining sinus rhythm seems to be partly offset by an increased mortality risk associated with antiarrhythmic drugs. The increasing attraction of stable sinus rhythm produced by successful percutaneous catheter ablation is, in no small measure, attributable to the hope that antiarrhythmic drugs may not be necessary.

There is ample data to suggest that current anticoagulant based stroke prevention therapy in AF patients is also sub-optimal. According to one study, barely half (53%) of high-risk patients with atrial fibrillation receive warfarin therapy when hospitalized [61]. Another analysis showed that a large proportion of AF patients at moderate to high risk for stroke do not receive guideline recommended thromboprophylaxis; and of those that do, many are not optimally controlled [62]. Most discouragingly, a Canadian study found that in patients with known AF *and* a prior stroke who were subsequently admitted with a second stroke, 15% were on no anticoagulation and only 18% were on warfarin and had a therapeutic INR [15].

In summary, AF represents a large and growing public health burden, with large gaps between best and usual care. For practitioners, managing care is complex and demanding; and, for patients, risk of significant morbidity and premature mortality are constant dangers.

1.2 Relevant New Knowledge

Fortunately, new and promising therapies and management strategies have recently emerged. In summary, they are:

- ***Radiofrequency catheter ablation.*** This technology has become more available and commonplace for treatment of AF since Haissaguerre et al. published their landmark paper [63, 64]. Ablation is primarily targeted at AF patients with paroxysmal or persistent atrial fibrillation that is anti-arrhythmic drug resistant and symptomatic, despite therapy with rate or rhythm control agents [65]. It can produce a cost-efficient and dramatic improvement in symptoms and quality of life [66].

- ***Antiarrhythmic drugs.*** One new agent in this class, dronedarone, was approved for use in AF therapy in December 2009; and, has been incorporated into the new CCS AF treatment guidelines largely because of its ability to effectively decrease hospitalizations and their associated costs [67-71]. However, some debate remains about the cost-effectiveness of the drug [71-74] and its scope of use has been recently narrowed [75-76].

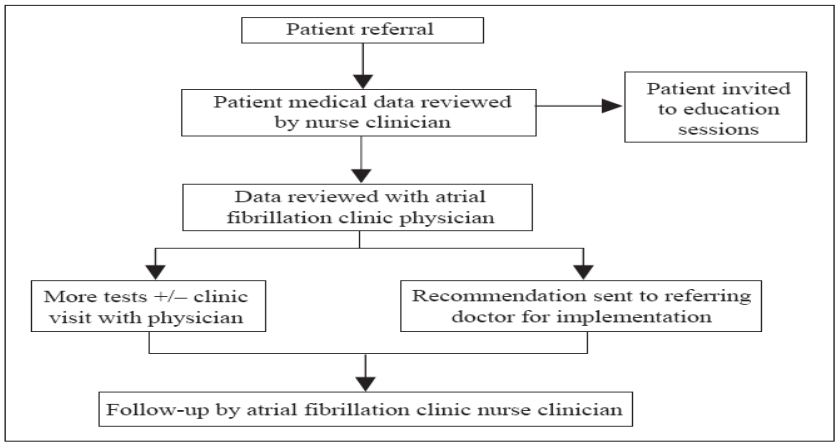
- ***Innovative oral anticoagulants.*** Warfarin has been the mainstay for oral anticoagulation for decades. However, there are very large gaps between optimal and actual applications of this therapy. For example, optimal warfarin-based therapy to reduce stroke risk is achieved by only 15% of outpatients and 53% of inpatients [15, 61].

  Very recently, large trials of 3 novel anticoagulant (NOAC) agents, dabigatran (a direct thrombin inhibitor), rivaroxaban and apixaban (both factor Xa inhibitors), in different populations of AF patients, have demonstrated these drugs to have a more favourable stroke prevention and bleeding profile than warfarin [77-79]. As compared with warfarin, all 3 drugs reduce the risk of stroke, particularly hemorrhagic stroke [77-79]. Moreover, the new drugs also share a similar tendency to reduce all-cause mortality risk [77-79].

- ***Health Social Networks: Team Care and AF Clinics.*** Lately, multi-disciplinary approaches to AF management, centred on specialty AF clinics, have been reporting encouraging results, especially markedly decreased wait times for specialist assessment and decreased number of

ER visits and hospitalizations, compared to the time before the introduction of this model of care [80]. The patient flow-through chart for the clinic is demonstrated in Figure 4.

Figure 4. Patient flow through the AF clinic in Calgary, Alberta, Canada



A clinical trial in the Netherlands reported a 33% reduction in CV hospitalizations, and more than a 70% relative risk reduction in cardiovascular mortality, with a nurse-led and cardiologist supervised AF clinic versus usual care [81, 132]. The beneficial outcomes from such care approaches are directionally similar to the successes reported with multidisciplinary, outpatient-based management of heart failure patients, leading to their widespread roll-out across the country [82-87]. And, new Canadian AF guidelines strongly reflect the value of a multidisciplinary management approach, including reduced wait times, greater coordination of care via nursing interventions, enhanced efficiency of resource utilization and better implementation of other cardiac therapies [55, 88-93].

– ***Clinical Decision Support Systems.*** Computerized Clinical Decision Support Systems (CDSS) are increasing in popularity within the health informatics (or health IT) industry; however, there are no standout systems at the primary care level for providers and patients in particular. The limited decision-support tools in the market today are largely bundled with large-scale health IT systems suitable for tertiary care hospitals, with functionality limited to relatively simple procedures such as: triggers for care activities, alerts for drug prescriptions and allergies, disease diagnosis, drug prescriptions support and reminders for forthcoming events. Current systems are not based on computerized clinical guidelines and do not support long-term patient care, only episodic visits.

  This presents an opportunity to develop integrated and interactive CDSS that are knowledge-driven (based on clinical guidelines), agile in knowledge management and knowledge updatability, web- and smart-device accessible for broader outreach, targeted to primary care providers but also with provisions for nurse and specialist use, interactive educational tools for patients, able to handle multiple chronic diseases and even co-morbid diseases, integrate data streams from different sources and interoperate with existing

medical record systems, compliant to specialized clinical workflows and offer integrated patient care planning and surveillance capabilities.

Whether AF patient care and outcomes will improve at the population level with the implementation of one, or a combination, of these promising therapies and strategic care approaches remains uncertain.

1.3 Public Health and IMPACT-AF in Nova Scotia: A Synergy

As discussed above, AF is an important public health care issue and a growing priority of comparative effectiveness research [94]. The rationale for doing such work in Nova Scotia is compelling.

Nova Scotia provides a near-perfect real-world laboratory for health services and outcomes research seeking to identify alternative models of care. It has a population of approximately 940,000 [95], with one large academic centre and well-known referral patterns, that allow for the straightforward study of whole patient populations. It is especially suited for the study of cardiovascular diseases, whose prevalence in Nova Scotia is amongst the highest in Canada [96]. Moreover, Nova Scotia has one of the oldest populations in Canada, a desirable feature if the target disease is age-related, like AF.

The Nova Scotia geography provides an opportunity for study sites in diverse regions, with differing rural/urban mix, ensuring that successful test approaches are broadly portable, feasible and effective; yet travel distances are relatively short, thereby ensuring manageability and cost-efficiency. Nova Scotians are more ethnically homogeneous than many other provincial populations, serving to minimize racial differences in disease manifestations and outcomes, while also reducing some of the background effect of culture-specific approaches to care [97]. On the other hand, socio-economic disparities are broad, allowing, for example, insights into the utility of proposed interventions according to patient ability to pay [98].

The structure of the health care system in Nova Scotia is also conducive to health services research. The province is divided into 9 health care regions with some autonomy in service prioritization and delivery but, ultimately, all functioning as part of a single system. Tertiary cardiovascular diagnostic and therapeutic services for the entire province are centralised at the Queen Elizabeth II Health Sciences Centre (QEII HSC), the main teaching hospital of Dalhousie University, where virtually 100% of the provincial population requiring expert electrophysiological (EP) assessment or interventional services are referred. This facilitates significantly the process of tracking patient referrals, including any impediments to these, for EP consultation, AF ablation and other specialty-directed therapies.

In summary, Nova Scotia provides a unique environment for researching health services, outcomes, and alternative care models that are specific priority needs identified in the Canadian Heart Health Strategy [99] and by the Nova Scotia Department of Health and Wellness [100]. The Department of Health and Wellness has previously collaborated on successful multi-partner population health projects, including ICONS [101] and ANCHOR [102]. The participant

satisfaction [103], clinical effectiveness [104] and cost efficiencies [105,106] demonstrated by ICONS led, in fact, to its evolution from a research project to a publicly funded program – Cardiovascular Health Nova Scotia (CVHNS). CVHNS is a provincial program of the Nova Scotia Department of Health and Wellness which aims to improve the cardiovascular health and care of Nova Scotians. The Program's scope includes cardiac disease and stroke. CVHNS is responsible for:

- developing guidelines and service delivery models,
- working with District Health Authorities to improve cardiovascular health,
- monitoring and reporting cardiovascular health outcomes,
- facilitating professional development opportunities for health providers, and
- working with others to reduce the risk and burden of cardiovascular disease.

CVHNS is accountable to the Acute and Tertiary Care Branch of the Nova Scotia Department of Health and Wellness and receives advice from a Provincial Advisory Council. The Council advises the Program and subsequently the Department of Health and Wellness on pertinent health care issues and priorities related to Cardiovascular Health Nova Scotia's mandate. The Advisory Council consists of physicians, senior leaders from the District Health Authorities, researchers, health professionals, and non-governmental organizations.

The proposed project, IMPACT-AF, offers similar opportunities for demonstrating leadership in collaborative health policy research and the optimal translation of results to patient care.

2.0 Hypotheses

The main **hypothesis** is as follows:

In the primary care setting, implementation of a patient-centered, disease management platform, which supports practitioners and patients with evidence-based management strategies, including the optimal use of proven innovative therapies and repeated measuring and sharing of practices and outcomes information and education, will generate and reinforce beneficial behaviours to improve, and sustain, care and outcomes of AF patients in a cost effective manner.

2.1 Study Objective

The primary research question is:

Among community-based patients with AF, does providing an integrated Clinical Decision Support System (CDSS) to providers and patients improve process of care and clinical outcomes, and decrease the healthcare costs and resource utilizations over 12 months, as compared to usual care?

2.2 Study Outcomes

The **primary study outcome** is a composite of unplanned cardiovascular hospitalization at 12 months and AF-related emergency department visits.

Cardiovascular hospitalization is defined as the following:

Any unplanned hospitalization (admission with an overnight stay in hospital) due to one of the following causes: acute coronary syndrome, presyncope / syncope, transient ischemic attack / stroke, atrial fibrillation, flutter, pulmonary embolism / deep vein thrombosis /systemic embolism, worsening congestive heart failure including pulmonary edema or dyspnea of cardiac origin. [81,107]

The **primary safety outcome** is major bleeding.
Major bleeding is to be defined as fatal and/or symptomatic / intracranial bleeding in a critical area or organ, such as brain, intraspinal, intraocular, retroperitoneal, intra-articular or pericardial, or intramuscular with compartment syndrome and /or overt bleeding causing a fall in hemoglobin level of 20 g/L or more, or leading to transfusion of two or more units of whole blood or red cells. [108]

Secondary outcomes address clinical, process of care, quality of life, and cost effectiveness.

Clinical:

- Individual hospitalization elements as noted above.
- Any bleeding
- All cause mortality
- Appropriateness of oral anticoagulant therapy (based on current CCS guidelines, [23])

Process of Care:

- Access to specialist consultation
- Access to echocardiograms
- Access to catheter ablations for AF and atrial flutter

Health-related quality of life (HRQoL)

- HRQoL measured using the EQ-5D-5L questionnaire

Costs:

- The costs associated with the development, implementation, and maintenance of CDSS
- The costs associated with managing and treating patients with AF

Cost effectiveness

- Incremental cost effectiveness ratio between the interventional arm and the control arm

3.0 STUDY DESIGN

3.1 Description

The proposed project falls into the scope of what has been termed a pragmatic or practical clinical trial [109-111]. This means that the hypothesis and study design have been developed specifically to answer questions faced by policy makers as they seek to develop new and effective population health management approaches. The first goal is to develop a CDSS that has undergone preliminary assessment of its clinical usefulness by knowledge opinion leaders as well as practical field-testing of its utility and dependability in practice settings. Following this, a rigorous analytical assessment of efficacy will be undertaken.

Specifically, IMPACT-AF will include a prospective, randomized, unblinded cluster design clinical trial, proposed to take place within Nova Scotia over the time period of 2014-2018, that will investigate whether a Clinical Decision Support System (CDSS) improves the clinical outcomes of patients with AF. Primary care providers (n=200) will be randomized to usual care versus use of the CDSS in a 1:1 fashion, at the level of the clinic practice. In order to facilitate the study, primary care providers will be required to have high speed internet access. The study will follow patients over a minimum of 12 months after enrolment.

Patients Included in the Analysis:

1. Age >/= 18 years
2. Electrocardiographically confirmed atrial fibrillation or documentation of past diagnosis or management of AF in the patient's medical record
3. Able to provide informed consent in English
4. Resident of Nova Scotia

Exclusion Criteria:

1. Patients unable to provide informed consent
2. Patients who have a terminal illness and are not expected to be alive at the end of follow up.

3.2 Study Flow:

See Figure 5 for a Summary of Study Flow.

3.3 Usual Care

Primary care providers in the usual care arm will be asked to identify eligible patients from their practice and obtain informed consent for the patients to participate in the study. Aside from obtaining informed consent and completion of patient questionnaires there will be no other study specific intervention imposed on this arm. It is anticipated, that usual care will be provided according to current Canadian and international guidelines for the treatment and management of AF and represent the accepted standard care as established by the major medical specialty organizations dealing with AF management.

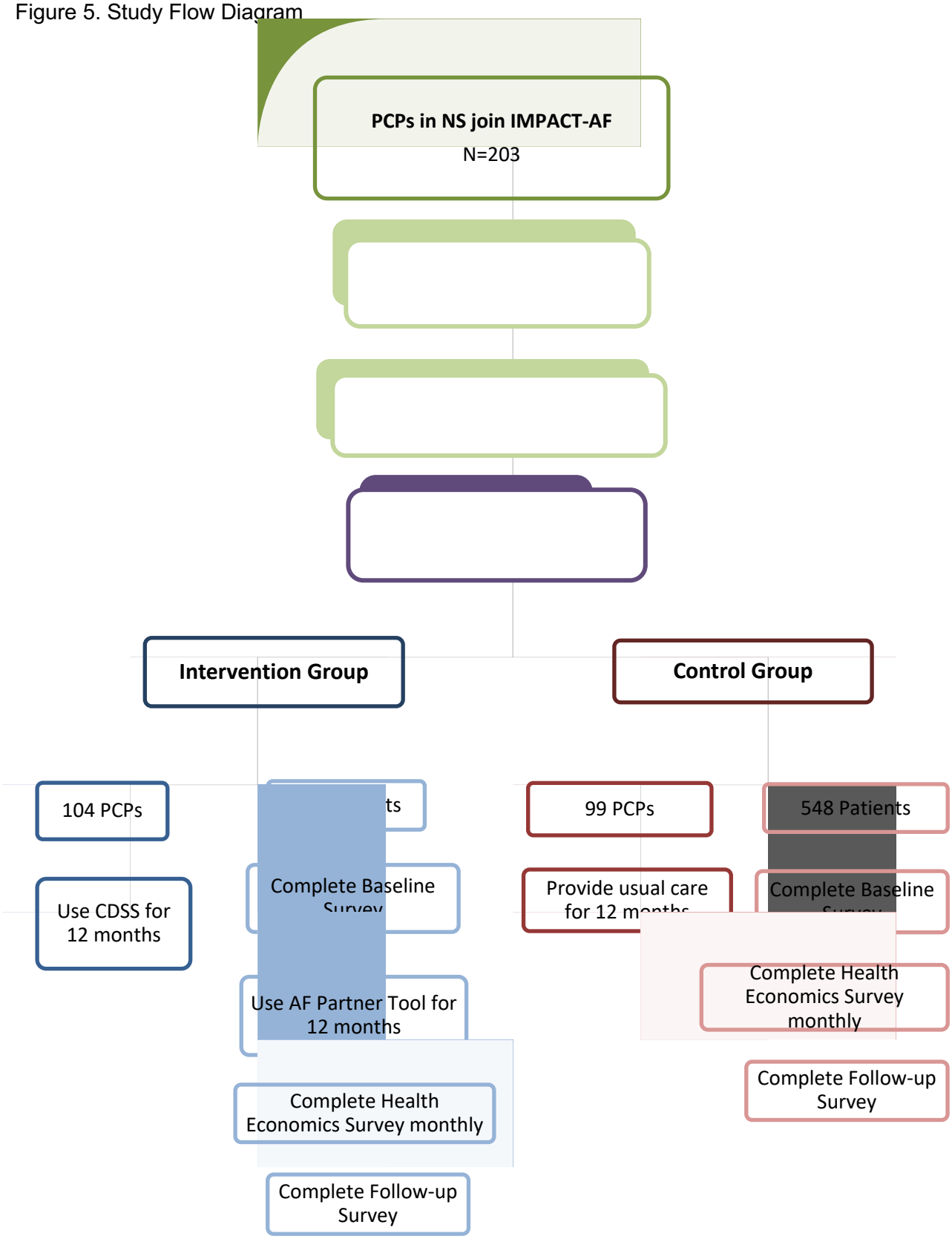
3.4 Intervention Arm

Participating practices in the intervention arm will receive access to the clinical decision support system (CDSS) intervention in their primary care setting. The CDSS is an integrated management system that involves many facets of the healthcare system. It will focus on four key elements:

1) Translation of best-evidence to Primary Care Providers (PCP) through computerized decision support aids designed to enable PCP to handle the identification and rapid treatment of AF patients at the primary care level;
2) Engagement and empowerment of patients in the self-management of their disease;
3) Remote surveillance of AF patients through a range of data streams with proactive response to critical trends and situations;
4) Leveraging innovative health informatics and computer science technologies to develop an integrated knowledge-centric patient-centered disease management platform (DMP).

Interventions most frequently cited as efficacious to improve care and outcomes in disease management include: stakeholder education and reminders of best care practices; financial incentives to follow best practices; and, regular measurement and feedback of actual practices and outcomes [101]. In the successful ICONS project, financial incentives were not used; instead, a combination of education, reminders and repeated measurement and feedback communication of practices and outcomes were all employed, including the sharing of region-specific and sub-group data [103-106].

Figure 5. Study Flow Diagram



Over the 5-year course of ICONS, it became evident that the network, itself, was also a likely efficacious intervention [104, 106]. Recent, basic science data support the observations and hypotheses generated by ICONS [112,113]. Briefly, this evidence suggests human behaviours are spread via networks of social contact, which add value by facilitation and reinforcement of beneficial behaviours. A few characteristics appear to be of key importance in relation to effectiveness. One is the number of reinforcing messages required to foster uptake of new behaviours, which will differ between individuals. This appears to be more important than who is delivering the message. Another is that the structure of the network also determines the extent and speed of behaviour adoption [113]. In this latter regard, the so-called clustered lattice network structure, which resembles the community-based organisation of ICONS, and is proposed for IMPACT-AF, is more efficient, or efficacious, than more random network structures [113].

For IMPACT-AF, we propose a broad community-based network of overlapping and shared interactions among providers, patients, their families and community-based referral services, all communicating with academic partners, patient advocacy organizations and policy makers in a clustered lattice type of network model integrated through a formalized electronic web. Such a network will facilitate the specific interventions outlined in Table 1 to overcome perceived impediments to optimal care.

Education will be provided to AF patients via the study website and paper-based materials included in patient mail outs. Similar to what was offered in ICONS, [101,103] stakeholder education will be offered via patient advocacy organizations, an IMPACT-AF Newsletter, web site and bi-annual meetings.

The academic hospital-based specialized clinic is planned to serve as an additional, albeit non-randomized comparator, of care. Indeed, it is hypothesized that the management and outcomes of community-based patients in the intervention arm of the IMPACT-AF study will not only be superior to what is seen in the usual care arm, but it will be as good as the care provided for those patients being managed uniformly through the specialized AF clinic.

Table 1. Barriers to optimal care and core interventions

Identified barriers	**Interventions**
Lack of knowledge	Interactive education sessions
Perception/reality mismatch	Audit and feedback
Lack of motivation	Network reinforcement
Beliefs/attitudes	Peer influence / opinion leaders
Systems of care	Process design

3.4.1 Proposed Technology Framework

This research program involves systemic integration of advance health informatics technologies, best evidence, health models and knowledge translation strategies and best evidence to develop a technology-assisted Atrial Fibrillation (AF) management framework. The project will adopt a knowledge management approach to both develop and deploy the proposed clinical decision support framework. The proposed research encompasses a patient-centered care delivery paradigm, targeting both patients and primary care physicians (PCP) that leverages state-of-the-art computer technologies to design personalized, interactive, pre-emptive, socially cognizant, contextually-aware, evidence-based AF strategies delivered through electronic media. A patient-centered approach to the translation of evidence into practice will be taken, addressing the knowledge gaps of PCP and the engagement of AF patients to develop a patient centered program of research and care delivery for the management of AF.

Our intent is to develop a four-layered research and care delivery program to address Atrial Fibrillation management as a longitudinal care process. The clinical care layer will investigate the theoretical framework of the Expanded Chronic Care Model to develop, implement and integrate innovative models of evidence-based patient care regarding Atrial Fibrillation into clinical practice. This model is well suited to this program because of the persistent nature of arrhythmic and thromboembolic issues over a lifetime and the link between AF and underlying chronic diseases such as chronic heart failure [114]. The patient engagement layer will investigate commitment and empowerment models (Social Cognition Theory, Health Belief Model and Shared Decision Making Model) to develop a high-level patient engagement model that can help us understand and establish patient perceptions on AF management in terms of personal goals, environmental, behavioural, functional and economic factors. The knowledge translation layer will build on the synergy of integrated knowledge translation models with web technologies to develop a collaborative, ubiquitous and immersive knowledge translation, sharing and training environment for PCP. The knowledge-modeling layer aims to leverage knowledge management methodologies to achieve the transformation and translation of paper-based clinical guidelines into knowledge-driven clinical decision support systems.

From an E-health research perspective, we will pursue the following research components:

1. Healthcare Knowledge Modeling
Healthcare knowledge modeling involves the abstraction and representation of medical concepts, relationships, constraints and rules to realize a formal computable knowledge model defining the domain [115, 116]. The model will be generic, scalable, robust and flexible and will serve as a generic logical and executable template for the computerization of multiple co-morbid guidelines in addition to AF guideline. Cutting edge Semantic Web technologies such as highly expressive and computer interpretable OWL-Web Ontology Language [117] will be used to model the health care knowledge as Ontology.

The model will be based on three different, yet interrelated knowledge objects as follows: (a) Clinical knowledge about AF management encapsulated within evidence-based clinical guidelines; (b) Behavior change strategies that are represented in terms of health behavior models—such as social cognition, health belief, shared decision making and so on; and (c) Clinical workflows that capture the function and operational workings of healthcare institutions, eliciting the processes, decisional choices and resources. These three unique knowledge objects will be modeled as three independent ontologies—namely the AF Knowledge Ontology, Behavior Strategy Ontology and Care Workflow Ontology—yet their active interplay based on our existing knowledge morphing method [118] will align these ontologies to renders a holistic knowledge base that will be used for AF decision support purposes.

2. Clinical Decision Support System for Primary Care Providers

Healthcare knowledge modeled in terms of specialized ontologies can be executed through CDSS to provide case-specific decision support [119,120]. In this project, we propose to build on our existing research covering the development of ontology-driven CDSS using Semantic Web Technologies [117,121] to develop a guideline-mediated AF CDSS to assist family physicians to manage patients with AF. Our approach is to leverage state-of-the-art Semantic Web technologies [117] that provide methods to systematically translate ontologically-modeled medical knowledge into point-of-care interventions. We will use a logic-based knowledge morphing method to integrate the different ontologies, explicating the domain and process-specific decision logic, conceptual constructs, process workflows and constraints in terms of explicit logical rules. We will employ OWL-based reasoning methods, using logic-based proof engines, to infer guideline-mediated patient-specific diagnostic and therapeutic recommendation based on specific patient information provided by the physician. The novelty of our decision support approach is that PCP can request justifications and explanations for the recommendations suggested by the CDSS. The AF CDSS will be accessible through a secure web portal over the internet (with potential for a mobile app).

3. Patient AF Self-Management Aids

This research program aims to deliver personalized, proactive and pervasive AF self-management and monitoring aids to help with self-management via health behavior change. In this regard, we propose to develop a mobile app – called AF Care Partner – that will feature a range of patient-specific AF self-management aids as follows:

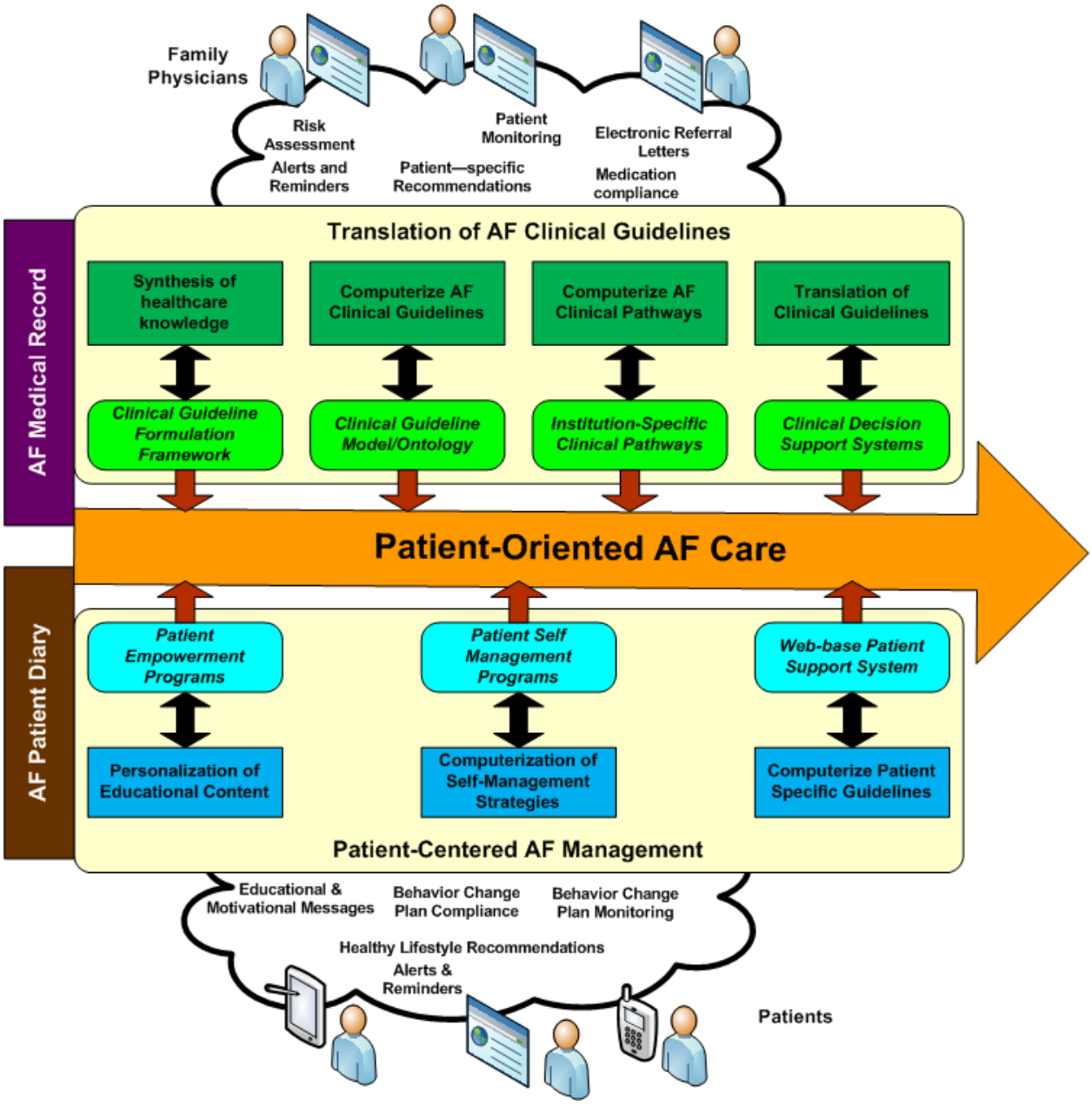
1. AF self-management plan adherence through (a) AF management goal setting and strategy design; (b) delivery of motivational, behaviour modification and emotion management educational messages; (c) vitals, diet, exercise, stress and mood recording diaries; (d) plan related alerts and reminders.

2. AF self-management plan monitoring through (a) weekly progress reports reflecting on goal attainment; (b) daily and weekly trends of risk factors based on diary data; (c) observed risk related alerts; (d) mood/stress related alerts.
3. Communication with care providers, with potential for peer support. Patients will be able to access the app through smart phones and tablets.

The project's deliverable will be a robust, scalable and flexible clinical decision support framework (Figure 6) for managing AF with a suite of enabling health informatics services. The short-term goal is to develop and implement care pathways for managing AF based on best evidence in primary care settings. This component will be designed prior to patient enrollment, with end-user testing of functionalities prior to the start of the clinical trial. The long-term goal is to extend design and functionality of the framework in order to incorporate and streamline patient-specific care pathways for multiple co-morbid diseases that commonly occur with AF. Once implemented, such a framework will be able to provide evidence-based decision support services for a wide range of co-morbid scenarios that are deemed treatable in the primary care setting. The project will impact health outcomes in terms of improving evidence-based care delivery, patient safety and satisfaction, care quality, patient-centeredness and cost / resource-effectiveness.

Anticipated challenges include: (a) Adoption of the intervention by Primary Care Providers (PCP); (b) Privacy and security of patient information that is collected and managed by the clinical decision support system; (c) Recruitment of PCP across the rural and urban regions of Nova Scotia; and, (d) Integration of the clinical decision support system with existing health IT systems.

Figure 6. CDSS Visual.



3.4.2 Other Interventions

A Change Management plan may be developed and deployed to ensure the technical solution (CDSS) is embraced, adopted and utilized effectively by providers and patients, so that the intended benefits (improved patient outcomes and enhanced patient and provider satisfaction) can be realized.

As per the Prosci® Change Management Process and ADKAR® Model, the 3 Phases of change will be addressed: Preparing for change, Managing Change and Reinforcing change™. Example activities would include: implementation of a readiness assessment, creation of a sponsorship model, change management plans developed to address ADKAR (Awareness, Desire, Knowledge, Ability and Reinforcement™) including plans for: Communication, Coaching, Training, Sponsor Roadmap and Resistance Management. Feedback would be collected and analyzed in order to diagnose gaps and or manage resistance. As necessary, corrective actions would be deployed and successes celebrated. (Prosci®, ADKAR®, Preparing for change, Managing Change and Reinforcing change ™ are trademarks of Prosci Inc. 2012).

3.5 Contamination and Co-intervention

Contamination of the usual care arm will be limited by having separate investigator meetings for PCPs enrolled into each arm. Discussion amongst PCPs that may occur outside of study meetings will not be able to be monitored, however this type of contamination is unlikely to have a significant impact on the usual care arm as they will not have access to the CDSS.

3.6 Sources of Bias

In cluster-randomized trials, there are important sources of bias to consider: recruitment bias, baseline imbalance and loss of clusters [122]. Recruitment bias should be limited as all patients in each PCP practice will be included, thereby minimizing bias in types of AF patients. Baseline imbalance is unlikely to be an issue as there are a large number of clusters in this study. Loss of clusters is possible but unlikely since there is little migration of PCPs from Nova Scotia; thus, loss of an entire cluster over the period of follow-up is improbable.

3.7 Study Procedures

3.7.1 Randomization

Primary care centres will obtain their randomized assignment (intervention versus control) at the time of recruitment. (See Section 4.0 for Study Recruitment Procedures.) Randomization will be stratified by whether the PCP is urban or rural. Urban is defined as a population $\geq$ 10,000, while rural is defined as < 10,000 population [123].

3.7.2 Treatment Period and Follow-up

The study will recruit PCPs until the goal of 200 is achieved, then follow patients for a minimum of 12 months. The intervention will be set up with appropriate training in the PCP practice prior to testing the intervention. There are no specific study visits for this trial; however, any unplanned PCP visits, emergency department visits and hospitalizations will be examined for important data (See Table 2).

3.7.3 Data Collection

Once informed consent has been obtained by the patient's PCP, a process to record retrospective baseline and ongoing clinical data prospectively will be implemented. Patients will be also requested to complete a patient case report form and quality of life questionnaire (either paper-based or electronic format) to gather relevant demographic and socioeconomic data. Acknowledging the age profile of AF patients in NS, it is anticipated that a proportion of

participants will chose not to complete online surveys or interact with the web-based tool. Completion of the web-based survey tools and / or interacting with the web-based tool, the AF Care Partner, is not mandatory for participation; all survey tools will be available to participants in a paper-based format.

In both study arms, baseline clinical data will be captured from the patient's chart by a data abstractor via on-site visit(s). Abstractors will utilize a laptop computer or tablet to record and transmit study data to secure and password protected servers located behind a firewall at Health Information Technology Services Nova Scotia (HITS-NS). This process will be repeated at 12 months for follow-up data collection in both study arms. Follow-up data for the intervention arm will also be captured through examination of data gathered during use of the CDSS.

The majority of patients at the start of the study are expected to have a past diagnosis of AF. As the study progresses, newly diagnosed patients are anticipated to be enrolled.

Review of PCP records will be done at 12 months to ensure completeness of outcome events. Clinical event / outcomes data will also be captured via review of hospitalization records for consented patients. Patients visiting the AF clinic in Halifax will be consented and data captured during their clinic visit. See Section 4.2 for further details.

Information to be collected on all patients will include contact details, demographic and socioeconomic characteristics, and, clinical, process of care and health outcome variables such as: Name, year and month of birth, health card number, mobile phone number, mailing address, internet access / smart-phone and social media usage, type of residence, gender, ethnicity, date of AF diagnosis, means of documentation of AF (ECG, Holter, other), medications, risk factors for AF, bleeding and stroke (based on HASBLED, CHADS2 and / or CHA2DS2-Vasc score), prior cardiovascular or other hospitalizations and ER / AF clinic / GP office visits for AF care, laboratory investigations (e.g., thyroid studies, renal function, hemoglobin, INR), referrals, alcohol use, smoking status, cardiac risk factors, other co-morbidities / past interventions and information on the patient's pharmacies of choice. Additional information that will be sought will relate to socioeconomic, quality of life and satisfaction with care (e.g., marital / employment status, annual household income, education level, care giver support, missed work, EQ-5D-5L questionnaire). See supporting data collection materials for a complete list of variables that will be captured from the patient and or the provider via Case Report / Data Collection Forms.

Table 2. Overview of variables collected during the study

Schedule Procedure	Initial Primary Care / AF Clinic Visit	Follow-up Visits	Tertiary Care (if applicable)
Visit date	X	X	X
Demographic data	X		
Medical history	X		
Investigations / Labs / Vital signs	X	X	X
Medications / Interventions	X	X	X
Socioeconomic / HRQoL	X	X	

Events (including details)	X	X	X

Costs
The relevant costs for this study may include the cost associated with the development, implementation, and maintenance of the CDSS. All the health care resource utilization associated with managing and treating participating patients with AF will also be recorded. This health care resource utilization may occur in the participating primary care providers and the tertiary AF care clinic.

HRQoL
HRQoL will be measured using health utility, a single index anchored at 0 representing death and 1 representing full health. Health utilities can be used to calculate quality adjusted life year (QALY) for economic evaluation. The EQ-5D is a prominent example of the utility-based instruments, with some indication that it has become the most widely used multi-attribute instrument in the world [124]. It consists of 5 dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension defines 3 levels indicating no problems (level 1), some problems (level 2), and extreme problems (level 3)(referred to as EQ-5D-3L) [123]. A new version of the EQ-5D has recently developed by refining the response options of the EQ-5D-3L to reflect 5 levels of impairment: no, slight, moderate, severe, and extreme problems in the five dimensions (the EQ-5D-5L) [125]. The EQ-5D-5L tends to improve descriptive richness and discriminatory power as it defines a total of 3125 health states compared to only 243 by the EQ-5D-3L. The EQ-5D-5L will be used in our study.

3.7.4 Data Quality
A Data Quality Coordinator will monitor data quality to ensure accuracy. This will be done via random audits of case report forms. All data captured in the study database will be validated at time of entry. Missing or implausible data will be queried.

3.7.5 Safety / Adverse Events
The IMPACT-AF study is not involved with examining novel therapies, but rather innovative approaches to optimizing proven, evidenced-informed care. Study outcomes such as bleeding will be monitored as a safety outcome, but a data safety and monitoring committee is not anticipated given the study is supporting uptake of Canadian guideline-based approaches to care.

3.8 Sample Size

The primary objective of the proposed study is a composite of unplanned cardiovascular hospitalizations in AF patients and any AF-related emergency department visits. The sample size calculation is based on the test of the null hypothesis that the percentages of patients with cardiovascular hospitalizations in the two populations (CDSS and usual care) are equal. The primary measure of effect is the difference in proportions of patients with composite of any AF-related emergency department visit or unplanned CV hospitalization over 12 months. The criterion for significance (alpha) has been set at 0.05. With the proposed sample size of 1075 primary care patients (537 per intervention/control arm, assuming a 1:1 allocation ratio), the study will have power of 80% to yield a statistically significant absolute difference of 10% (or 20 [RRR] relative risk reduction) between the two percentages of patients with composite of any AF-related emergency department visit or unplanned CV hospitalization in the control and intervention groups, assuming 50% annual rate of CVD hospitalizations for the control group. This sample size was adjusted for a potential clustering of patient outcomes within a physician, by assuming an intra-physician correlation coefficient (ICC) of 0.05 with an average cluster size of 9 patients/physician. The ICC is based on studies done in the primary care sector reporting this magnitude of ICC. This extent of reduction was felt to represent a minimal clinically important achievement by a consensus of study investigators and has been an endpoint target in other studies in AF populations of similar design [127-129].

Table 3 provides a summary of the sample size calculation for different values of the baseline control rate (50%, 58%), RRR (15%, 20%, 25%, 30%), intra-class correlation coefficient [ICC] (0.05, 0.10) and average cluster size (m) (9,12,15). The primary measure of effect is the difference in the proportions or percentages of patients with cardiovascular hospitalizations and AF-related emergency room visits across study arms over an active study period of 12 months. The criterion for significance (alpha) has been set at 0.05. The test is 2-tailed, which means that an effect in either direction will be interpreted. The statistical power is set at 80%.

The above computation assumes a binomial distribution for the number of patients with cardiovascular hospitalizations and AF-related ED visits, a baseline control rate of about 50% and hypothesized RRR of 20%. We also adjusted the sample size for a potential clustering of patient responses within a practice group, varying the intra-class correlation coefficient (ICC)—which measures the degree of clustering – from 9-15 (see Table 3). Therefore, the required sample size of 1075 patients corresponds to an ICC of 0.05 and average cluster size of m= 9.

P0= the proportion of patients in the control group
MCID=minimal clinically important difference/improvement
P1=proportion in the intervention group
n=Total unadjusted sample size
ICC=intra-cluster/practice correlation coefficient
m=average cluster size
VIF=1+(m-1)ICC=variance inflation factor
n_adj=n*VIF=Total adjusted sample size (adjusted for clustering)
RRR = relative risk reduction

The calculations are based on

Control rate of 50% and 58% based on the NS data
RRR varying from 15% to 30%
Average cluster sizes (m) of 20, 25 and 30
ICC values of 0.05 and 0.10
Alpha = 0.05 Beta = 0.20

Table 3. Sample size Calculation

P0	RRR	MCID	P1	n	ICC	m	VIF	n_adj	k
0.58	0.3	0.174	0.406	251.0602299	0.05	9	1.4	351.4843218	**39.05381354**
0.58	0.3	0.174	0.406	251.0602299	0.05	12	1.55	389.1433563	**32.42861303**
0.58	0.3	0.174	0.406	251.0602299	0.05	15	1.7	426.8023908	**28.45349272**
0.58	0.25	0.145	0.435	364.9655172	0.05	9	1.4	510.9517241	**56.77241379**
0.58	0.25	0.145	0.435	364.9655172	0.05	12	1.55	565.6965517	**47.14137931**
0.58	0.25	0.145	0.435	364.9655172	0.05	15	1.7	620.4413793	**41.36275862**
0.58	0.2	0.116	0.464	573.6717241	0.05	9	1.4	803.1404138	**89.23782375**
0.58	0.2	0.116	0.464	573.6717241	0.05	12	1.55	889.1911724	**74.09926437**
0.58	0.2	0.116	0.464	573.6717241	0.05	15	1.7	975.241931	**65.01612874**
0.58	0.15	0.087	0.493	1022.444138	0.05	9	1.4	1431.421793	**159.0468659**
0.58	0.15	0.087	0.493	1022.444138	0.05	12	1.55	1584.788414	**132.0657011**
0.58	0.15	0.087	0.493	1022.444138	0.05	15	1.7	1738.155034	**115.8770023**
0.58	0.3	0.174	0.406	251.0602299	0.1	9	1.8	451.9084138	**50.21204598**
0.58	0.3	0.174	0.406	251.0602299	0.1	12	2.1	527.2264828	**43.93554023**
0.58	0.3	0.174	0.406	251.0602299	0.1	15	2.4	602.5445517	**40.16963678**
0.58	0.25	0.145	0.435	364.9655172	0.1	9	1.8	656.937931	**72.99310345**
0.58	0.25	0.145	0.435	364.9655172	0.1	12	2.1	766.4275862	**63.86896552**
0.58	0.25	0.145	0.435	364.9655172	0.1	15	2.4	875.9172414	**58.39448276**
0.58	0.2	0.116	0.464	573.6717241	0.1	9	1.8	1032.609103	**114.7343448**
0.58	0.2	0.116	0.464	573.6717241	0.1	12	2.1	1204.710621	**100.3925517**
0.58	0.2	0.116	0.464	573.6717241	0.1	15	2.4	1376.812138	**91.78747586**
0.58	0.15	0.087	0.493	1022.444138	0.1	9	1.8	1840.399448	**204.4888276**
0.58	0.15	0.087	0.493	1022.444138	0.05	12	1.55	1584.788414	**132.0657011**
0.58	0.15	0.087	0.493	1022.444138	0.05	15	1.7	1738.155034	**115.8770023**
0.5	0.3	0.15	0.35	332.7644444	0.05	9	1.4	465.8702222	**51.76335802**
0.5	0.3	0.15	0.35	332.7644444	0.05	12	1.55	515.7848889	**42.98207407**
0.5	0.3	0.15	0.35	332.7644444	0.05	15	1.7	565.6995556	**37.7133037**
0.5	0.25	0.125	0.375	486.08	0.05	9	1.4	680.512	**75.61244444**
0.5	0.25	0.125	0.375	486.08	0.05	12	1.55	753.424	**62.78533333**
0.5	0.25	0.125	0.375	486.08	0.05	15	1.7	826.336	**55.08906667**
0.5	0.2	0.1	0.4	768.32	0.05	9	1.4	1075.648	**119.5164444**
0.5	0.2	0.1	0.4	768.32	0.05	12	1.55	1190.896	**99.24133333**
0.5	0.2	0.1	0.4	768.32	0.05	15	1.7	1306.144	**87.07626667**
0.5	0.15	0.075	0.425	1378.097778	0.05	9	1.4	1929.336889	**214.3707654**
0.5	0.15	0.075	0.425	1378.097778	0.05	12	1.55	2136.051556	**178.0042963**
0.5	0.15	0.075	0.425	1378.097778	0.05	15	1.7	2342.766222	**156.1844148**
0.5	0.3	0.15	0.35	332.7644444	0.1	9	1.8	598.976	**66.55288889**
0.5	0.3	0.15	0.35	332.7644444	0.1	12	2.1	698.8053333	**58.23377778**
0.5	0.3	0.15	0.35	332.7644444	0.1	15	2.4	798.6346667	**53.24231111**
0.5	0.25	0.125	0.375	486.08	0.1	9	1.8	874.944	**97.216**
0.5	0.25	0.125	0.375	486.08	0.1	12	2.1	1020.768	**85.064**
0.5	0.25	0.125	0.375	486.08	0.1	15	2.4	1166.592	**77.7728**
0.5	0.2	0.1	0.4	768.32	0.1	9	1.8	1382.976	**153.664**

3.9 Statistical Analysis:

The analysis and reporting of the trial results will follow the CONSORT Statement for cluster-randomization trials [129]. The baseline characteristics of the practices and patients will be reported by group as mean (standard deviation) or median (first quartile, third quartile) for continuous variables, depending on the distribution, and count (percent) for categorical variables. The analysis will follow the intention-to-treat (ITT) principle. The unit of randomization will be the practice. The unit of analysis will be the patient. We will use multiple imputation to handle missing data to enable ITT analysis. Multiple imputation is a Monte Carlo technique in which the missing values are replaced by m > 1 simulated versions, where 'm' is typically small. Each of the simulated complete datasets will be analyzed by standard methods, and the results will be combines to produce estimates and confidence intervals that incorporate missing data uncertainty [133]. We will use generalized estimating equations (GEE) – assuming exchangeable correlation structure for patients within the same practice, and adjusting for urban and rural practice types to analyse all outcomes [130]. Unlike ordinary regression techniques, GEE allows us to model the intra-practice correlation among patients within each practice. The results will be reported as the estimate of the effect, corresponding 95% confidence interval and associated p-values. All p-values will be reported to three decimal places with those less than 0.001 reported as p<0.001. The criterion for statistical significance will be set a priori at alpha = 0.05, and adjusted using the Bonferroni method for multiple secondary analyses. All analyses will be performed using SAS 9.4 (Cary, NC).

Sensitivity analyses: 1) There are several methods for analyzing cluster RCTs [131]. Therefore, we will perform sensitivity analyses using some of the commonly used patient-level methods such as random-intercept model and cluster-level (i.e. random- and fixed-effects meta-analytic) methods to assess the robustness of the results. 2) Given that the unit of randomization is the practice, there is a higher chance of potential imbalance of patient-level baseline characteristics. We will perform some sensitivity analysis to adjust for any potential imbalance.

HRQoL

The proportion of patients with reported impairment in each of the five EQ-5D-5L dimensions will be calculated for each arm. Health utilities will be calculated using the Canadian EQ-5D-5L scoring algorithm. QALYs accumulated over the study period will be calculated using the area under the curve method.

Costs

Total cost will be calculated using the sum of the product of resource utilization items (e.g. length of hospital stay, medications) and corresponding unit costs.

Cost effectiveness

The incremental cost effectiveness ratio (ICER) will be calculated by dividing the incremental difference in the mean cost between the treatment arms by the incremental difference in the mean QALYs between the arms. Sampling uncertainty is a critical issue that needs to be sufficiently and adequately dealt with in any economic evaluation alongside a clinical trial.

Nonparametric bootstrap with replacement will be used to estimate the confidence intervals around the ICER. The decision uncertainty will be presented using the cost effectiveness acceptability curves in which maximum willingness to pay value from the policy maker's perspective is explicitly considered. Both base case and uncertainty analyses will be stratified by demographic and socioeconomic variables (such as age, gender and income). These stratified analyses are important for any economic evaluation to identify subpopulations that could potentially receive the most benefit from the intervention.

4.0 Study Population

4.1 Recruitment of Clinics and Practitioners Managing AF Patients

IMPACT-AF will seek participation from a wide variety of primary care providers managing AF patients within Nova Scotia. All patients with a prior or new electrocardiographically confirmed diagnosis of AF during the study period will be eligible for inclusion as part of the study.

Inclusion Criteria: Any licensed medical provider of community-based adult patients with a minimum of 15 diagnosed AF patients enrolled in the study from their practice will be eligible to participate. To avoid bias based on technological availability or proficiency, all eligible providers are required to have access to high-speed internet access in their office for the duration of this study. As well, participating providers must sign a site agreement which outline the following terms:

- Agree to participate for the duration of the study;
- Notify the research team if your practice:
    - Is located in an urban (population ≥10,000) or rural (population < 10,000) setting; and,
    - Operates as a collaborative practice (i.e., shares in the care of patients with at least one other health care provider);
- Attend and participate in investigator meetings;
- Identify <u>all eligible</u> patients in your practice who meet the study inclusion criteria;
- Invite all eligible participants to join in the study (either in person or via mail outs);
- Perform informed consent discussions with eligible participants who visit your practice for routine care;
- Accept randomization into either the control or intervention group;
- Agree to store informed consent forms and completed patient questionnaires in locked filing cabinets in an access-controlled location within your practice (after faxing a copy to the study office);
- Agree to be trained on and use the web-based decision support tool, if assigned to the intervention group;
- Allow the study team access to medical records for consented study participants at baseline and follow-up;
- Facilitate the distribution of patient questionnaires (all materials supplied by the research team);

- Notify the Privacy Officer at HITS-NS that the study team is to be granted access to data for all patients who consent to study inclusion and provide copies of patient signed consent forms as requested.
- Report any problems that you experience related to your participation in the study.
- Agree not to disclose or use any study related information for purposes other than the delivery of standard AF patient care and study activities.
- Agree that all information disclosed by the research team regarding the study will be considered confidential information and not disclosed, publish or disseminated to any third party other than your employees (e.g., nursing and administrative staff).

Exclusion Criteria: Providers who do not meet the above criteria will be excluded from the study.

Provider Recruitment: Doctors Nova Scotia, the medical association for Nova Scotia physicians, has been invited to identify a primary care physician to participate as a peer Champion on the project Advisory Committee. Doctors Nova Scotia and the peer champion will also be engaged and consulted to support primary care provider recruitment across Nova Scotia. Proactive provider recruitment activities are expected to include: electronic and paper-based notices (e.g., in the Doctors Nova Scotia magazine and other relevant discipline-based publications / websites), letters of invitation to participate (fax, e-mail and or hard-copy via hospital mail-boxes) sent to all primary care practices across Nova Scotia, study display booths at local medical conventions, face-to-face information sessions during community based CME events, and at specific provider meetings (e.g., family practice meetings). Recruitment will begin following confirmation of ethics approval and is anticipated to continue for 6 months, or until the desired number of practices is achieved. Promotional study materials (e.g., branded brochures, post-card, wall posters, FAQ documents, study website) will be used during the provider recruitment phase.

4.1.1 Pharmacist Participation: Consented patients will be requested to identify those pharmacies which they frequent for their medication needs. With the patient's consent, individual pharmacies will be notified by the Project Office that the patient is an IMPACT-AF study participant and invited to visit the study website for further details on the study. Pharmacy directed communications are also anticipated via regular communication channels (e.g., pharmacy websites, newsletters, etc).

4.2 Patient ID / Recruitment / Inclusion / Exclusion

Primary Care ID / Recruitment: Provider recruitment will aim to be broad to help ensure that the findings of the study can be generalized. Based upon NS billing data, the average family practice in NS is estimated to have between 20-30 adult (aged $\geq$ 18 years) patients with diagnosed AF. Practices will be provided with detailed written and verbal instructions on patient identification methods during the investigator orientation session entitled 'How to Create an AF Patient Registry'. EMR or billing systems can be queried (e.g., search for: ICD-9 diagnostic code 427.3 (atrial fibrillation) and or 427 (Cardiac dysrhythmias) OR ICD-10 code I48 (atrial

fibrillation and flutter) billings in the last 24 months, AF diagnosis in the past history or problem list, INR monitoring / flow sheet use, use of specific medications, etc.), as well as paper-based methods utilized (e.g., tracking patients on a daily basis or using stickers / index cards) to identify potential patients with AF. Practices will be asked to create and maintain a confidential electronic registry of patient names, preferably versus a paper-based registry, that can track relevant clinical information on AF for both the practice and IMPACT-AF purposes. The expectation is for participating practices to explore their total patient population for patients with AF, not just those known to have the condition.

Other options for patient identification include: providers can request from MSI a list of those patients whom the provider has billed for an AF-related visit or INR monitoring in the last 12-24 months. Project support staff, or other peer champions, will be available after investigator orientation to support practices requiring assistance in patient identification, consenting and registry creation.

Once eligible patients are identified, a consent brochure will be mailed or handed to the patient. If the patient is seen in the provider's office, consent will be sought at the time of visit. Each patient will be assigned a study number for coding purposes; otherwise, unique identifiers for health record identification and linkage will remain with the health facility at which they were recruited and where their AF care is routinely provided. This affords a mechanism to allow follow-up on long-term care procedure and events through subsequent chart review or database linkage without having to include unique health identifiers in the IMPACT-AF study registry.

AF Clinic ID / Recruitment: Patients visiting the AF Clinic at the QEII Health Science Centre will also be asked to participate and sign a consent form. The patient's primary care provider would be notified that the patient has agreed to participate via the AF clinic site.

Inclusion Criteria:
Primary Care: All new and previously diagnosed patients ≥ 18 years of age with AF and a life expectancy > 12 months will be eligible for study enrollment. In addition, patients will need to be:

- A registered and regular patient at a primary care practice participating in the IMPACT-AF study;
- Able to read, understand and communicate in English.
- A resident of Nova Scotia.

Patients in the Intervention Arm will have the option to interact with the CDSS through the patient portal, the AF Care Partner tool. These patients will therefore need access to the Internet and be willing to input information and receive feedback and reminders from the AF Care Partner tool over the duration of the study. Patients can revoke their AF Care Partner tool participation if desired.

All AF Clinic (QEII HSC) patients will be invited to participate in the IMPACT-AF study by signing an informed consent form.

Exclusion Criteria: Patients with a terminal illness (expected death within 12-months) and those having cognitive impairment or who are unable to communicate in English will be considered ineligible for participation. Also ineligible for inclusion are AF patients whose care is being significantly overseen by a specialist as well as those who are patients of the hospital-based AF clinic at the QEII Health Sciences Centre.

4.3 Ethical Considerations

IMPACT-AF is a non-interventional study. There is no assignment of a patient to a particular therapeutic strategy; instead, the treatment decision falls within the boundaries of acceptable current practice and treatment options remain the decision of the primary care provider.

Ethics approval will be solicited through the Nova Scotia Multisite Research Ethics Board. Providers will be required to sign a site agreement. Patient consent will also be sought from all participants at the beginning of their involvement in the study. Consent forms will be standardized to adhere to local ethics criteria and good clinical practices, with reference to all planned data capture including clinical, demographic, socioeconomic, economic and health care utilization information. The consent process will be as previously outlined.

Provider and patient confidentiality will be maintained via encryption of all electronic study data. Only Canadian servers will be utilized to host the study registry and clinical decision support system with the servers housed at the Nova Scotia government's provincial data center. The CDSS, AF Care Partner and participant data will be stored on firewall and password protected servers located at HITS-NS. A unique Study ID is created for each patient following enrollment in the study. A participant registry stores the name and corresponding Study ID for each participant. All study data collected will be stored by Study ID and names will be removed and kept separate from the participant registry. The intervention tool (CDSS) will also be stored on servers at HITS-NS; when a Primary Care Provider and / or patient interacts with the intervention tool, all data is immediately sent and stored on these servers.

All study researchers, staff, Site Investigators and participants will access the servers through a secure login requiring unique usernames and passwords. Individuals will be permitted access to only the information required for their role in the study.

Hard copy study forms maintained at the Study Coordinating Centre (e.g., any patient data or AF clinic consent forms, etc) will be maintained in a secured locked cabinet in a secure location on the QEII HSC property.

5.0 STUDY ORGANIZATION

5.1 Medical Experts

Medical Experts for the study are:

- Dr. Jafna Cox
- Dr. Ratika Parkash
- Dr. Jim MacKillop (family physician)

5.2 Health Informatics Experts
Health Informatics Experts for the study are:
- Dr. Raza Abidi
- Dr. Samina Abidi

5.3 Statistician Expert
Statistician Expert for the study is:
- Dr. Lehana Thabane

5.4 Health Economist Expert
Heath Economic Expert for the study is:
- Dr. Feng Xie

5.5 Committees
IMPACT-AF will be organized similar to other successful health management / clinical studies. See Appendix 6.1

5.5.1 Executive Committee:

The project Executive Committee is responsible for study oversight. Participation includes:
- Dr. Jafna Cox, Dr. Raza Abidi, Dr. Ratika Parkash, Dr. Samina Abidi, Dr. Lehana Thabane, Dr. Feng Xie, Dr. Jim MacKillop;
- NS Department of Health and Wellness; and,
- Dr. Shurjeel Choudhri, Bayer.

A Project Chairperson from the investigator team will be responsible for overall project supervision and chairing of all committee meetings. Executive Committee members are expected to: actively participate in committee meetings; respect confidentiality of all information discussed; serve for the duration of the project, but may resign by providing the Committee Chair with written notice two months in advance of the effective date of their resignation. Each member has one vote on committee decisions. The quorum for all meetings shall consist of a majority of the voting members in attendance. Committee expenses / honoraria, if applicable, are provided from within the project budget.
- Mandate: Responsible for overall project governance including all operational and budget issues.
    - The Project Office coordinates day-to-day management issues.
- Meets frequently, usually bi-monthly at project start and monthly thereafter (or as required). Meeting minutes will serve as record of Committee activities to be distributed within 15 days following the meeting.
- Reports to the Advisory Committee.
- Administrative support provided by the Project Office.

5.5.2 Advisory Committee:

The project Advisory Committee, a broad-based, multi-stakeholder group reflective of all partners, will be responsible to provide expertise, guide strategic decisions, inform and communicate with their representative organization(s) regarding project development, implementation, evaluation and or knowledge translation. This committee of 15-20 participants is expected to include representatives from:

- NS Department of Health and Wellness/Provincial Programs
- Heart and Stroke Foundation Nova Scotia
- Patient representative
- Doctors Nova Scotia
- Pharmacy (retails chains, independents and or the Association)
- Long Term Care organization(s)
- Bayer Healthcare
- Clinical Advisors (Neurology / Hematology / Geriatrics)
- Canada Health Infoway
- Health IT vendors (TELUS Health)
- Canadian Cardiovascular Society
- Provider representatives (FPN, NP or RN rep)
- NS Health Research Foundation
- One or more District Health Authority representatives
- Other participants may be added e.g. NSCAD.

Advisory Members are expected to: actively participate in committee meetings; respect confidentiality of all information discussed, as appropriate; serve for the duration of the project, but may resign by providing the Committee Chair with written notice two months in advance of the effective date of their resignation. Each member has one vote on committee decisions. The quorum for all meetings shall consist of a majority of the voting members in attendance. Committee expenses / honoraria, if applicable, are provided from within the project budget.

- Mandate: Concerned with project development, providing input, guidance and direction on the project, its goals, implementation and any major policy issues / decisions. Responsible for promoting and driving the project in their organizations and across the province.
- Meetings twice yearly.
- Meeting minutes will serve as record of Committee activities to be distributed within 30 days / months following each meeting.
- Administrative support provided by the Project Office.

5.5.3 Adjudication Committee:

An adjudication committee may be created to provide oversight regarding adjudication of certain study outcomes. Anticipated members include: a clinical cardiologist, an electrophysiologist, a neurologist and a haematologist. The committee will be blinded to

treatment allocation if applicable. Meetings will be held as needed subsequent to the collection of data.

5.5.4 External Review Committee:

An external review committee of 4-5 participants may be created to provide visionary oversight and peer-review on a yearly basis. Consideration will be given to non-Nova Scotia, non-Canadian participants. Representatives are likely to include computer scientists, clinical experts, knowledge translation researchers, health services researchers, and health policy makers or researchers.

5.5.5 Other Committees

Other project collaborators / co-investigators (e.g., subject matter experts) are expected to participant in additional project committees (e.g., Technology Development, Sub-Studies, Economics and Knowledge Translation). Participants may include:

- Health Economist, Behavior / Health Psychologist, Communications / Media (e.g., Dalhousie Faculty of Management), Adult / Health Education, Computer Science – Human Interaction
- Membership: Composed of a core group of individuals with particular subject matter expertise.
    - Members are expected to: actively participate in committee meetings; respect confidentiality of all information discussed, as appropriate; serve for the duration of the project, but may resign by providing the Committee Chair with written notice two months in advance of the effective date of their resignation.
    - Ad hoc members as required.
    - Each member has one vote on committee decisions. The quorum for all meetings shall consist of a majority of the voting members in attendance. Committee expenses / honoraria, if applicable, are provided from within the project budget.
- Mandate: Charged with providing subject matter expertise regarding project-related issues / implications of the study.
- Meets as required to address planning and discuss results of economic evaluations. Meeting minutes will serve as record of Committee activities to be distributed within 15 days following the meeting.
- Administrative support provided by the Project Office.

8.0 REFERENCES

1. Camm AJ, Obel OA. Epidemiology and mechanism of atrial fibrillation and atrial flutter. *Am J Cardiol* 1996; 78 (8A): 3-11.

2. Lip GY, Tse HF. Management of atrial fibrillation. *Lancet* 2007; 370(9587):604-618.

3. http://www.heartandstroke.com/site/c.ikIQLcMWJtE/b.5052135/k.2C86/Heart_disease__Atrial_fibrillation.htm; accessed June 7, 2011.

4. Miyasaka Y et al. *Circulation*. 2006; 114: 119-125.

5. Santini M, Ricci RP. The worldwide social burden of atrial fibrillation: what should be done and where do we go? *J Interv Card Electrophysiol* 2006; 17: 183-8.

6. Lloyd-Jones, D., et al., *Heart disease and stroke statistics--2010 update: a report from the American Heart Association.* Circulation, 2010. **121**(7): p. e46-e215.

7. Wolf PA, Dawber TR, Thomas HE, Jr., Kannel WB. Epidemiologic assessment of chronic atrial fibrillation and risk of stroke: the Framingham study. *Neurology* 1978; 28(10):973-977.

8. Wolf PA, Abbott RD, Kannel WB. Atrial fibrillation: a major contributor to stroke in the elderly. The Framingham Study. *Arch Intern Med* 1987; 147(9):1561-1564.

9. Benjamin EJ, Wolf PA, D'Agostino RB, Silbershatz H, Kannel WB, Levy D. Impact of atrial fibrillation on the risk of death: the Framingham Heart Study. *Circulation* 1998; 98(10):946-952.

10. Vidaillet, H., et al., *A population-based study of mortality among patients with atrial fibrillation or flutter.* Am J Med, 2002. **113**(5): p. 365-70.

11. Atrial Fibrillation Investigators: Atrial Fibrillation, Aspirin, Anticoagulation Study; Boston Area Anticoagulation Trial for Atrial Fibrillation Study; Canadian Atrial Fibrillation Anticoagulation Study; Stroke Prevention in Atrial Fibrillation Study; Veterans Affairs Stroke Prevention in Nonrheumatic Atrial Fibrillation Study. Risk factors for stroke and efficacy of antithrombotic therapy in atrial fibrillation. Analysis of pooled data from five randomized controlled trials. *Arch Intern Med* 1994; 154(13): 1449-1457.

12. Wolf PA, Abbott RD, Kannel WB. Atrial fibrillation as an independent risk factor for stroke: the Framingham Study. *Stroke* 1991; 22; 983-988.

13. Savelieva I, Bajpai A, Camm AJ. Stroke in atrial fibrillation: update on pathophysiology, new antithrombotic therapies, and evolution of procedures and devices. *Ann Med* 2007; 39(5): 371-91.

14. Singer DE, Albers GW, Dalen JE, Fang MC, Go AS, Halperin JL, Lip GY, Manning WJ; American College of Chest Physicians. Antithrombotic therapy in atrial fibrillation: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). *Chest* 2008 Jun;133(6 Suppl):546S-592S.

15. Gladstone DJ, Bui E, Fang J, Laupacis A, Lindsay MP, Tu JV, Silver FL, Kapral MK. Potentially preventable strokes in high-risk patients with atrial fibrillation who are not adequately anticoagulated. *Stroke* 2009; 40(1): 235-240.

16. Dorian P, Jung W, Newman D, et al. The impairment of health-related quality of life in patients with intermittent atrial fibrillation: implications for the assessment of investigational therapy. *J Am Coll Cardiol* 2000; 36(4): 1303-9.

17. Dorian P, Cvitkovic SS, Kerr CR, Crystal E, Gillis AM, Guerra PG et al. A novel, simple scale for assessing the symptom severity of atrial fibrillation at the bedside: the CCS-SAF scale. *Can J Cardiol* 2006; 22(5): 383-386.

18. Dorian P, Guerra PG, Kerr CR et al. Validation of a new simple scale to measure symptoms in atrial fibrillation: the Canadian Cardiovascular Society Severity in Atrial Fibrillation scale. Circ Arrhythm Electrophysiol. 2009 Jun;2(3):218-24

19. Singh SN, Tang XC, Singh BN, et al. Quality of life and exercise performance in patients in sinus rhythm versus persistent atrial fibrillation: a Veterans Affairs Cooperative Studies Program Substudy. *J Am Coll Cardiol* 2006. 48(4): 721-30.

20. Wattigney WA, Mensah GA, Croft JB. Increasing trends in hospitalization for atrial fibrillation in the United States, 1985 through 1999: implications for primary prevention. *Circulation* 2003; 108(6): 711-6.

21. McDonald AJ, Pelletier AJ, Ellinor PT, Camargo CA, Jr. Increasing US emergency department visit rates and subsequent hospital admissions for atrial fibrillation from 1993 to 2004. *Ann Emerg Med* 2008; 51(1): 58-65.

22. Humphries K, Jackevicius C, Gong Y, Svensen L, Cox J, Tu J, Laupacis A. Population rates of hospitalization for atrial fibrillation/flutter in Canada. *Can J Cardiol* 2004; 20(9): 869-876.

23. Cairns JA, Connolly S, McMurtry S, Stephenson M, Talajic M. Canadian cardiovascular society atrial fibrillation guidelines 2010: prevention of stroke and systemic thromboembolism in atrial fibrillation and flutter. *Can J Cardiol* 2011; 27(1): 74-90.

24. Gillis AM, Verma A, Talajic M, Nattel S, Dorian P. Canadian cardiovascular society atrial fibrillation guidelines 2010: rate and rhythm management. *Can J Cardiol* 2011; 27(1):47-59.

25. Khaykin Y, Morillo CA, Skanes AC, McCracken A, Humphries K, Kerr CR. Cost comparison of catheter ablation and medical therapy in atrial fibrillation. *J Cardiovasc Electrophysiol* 2007; 18(9):907-913.

26. Schulman S, Anderson DR, Bungard TJ, Jaeger T, Kahn SR, Wells P, Wilson SJ. Direct and indirect costs of management of long-term warfarin therapy in Canada. *J Thromb Haemost* 2010; 8: 2192–2200.

27. Coyne KS, Paramore C, Grandy S, Mercader M, Reynolds M, Zimetbaum P. Assessing the direct costs of treating nonvalvular atrial fibrillation in the United States. *Value Health* 2006; 9(5):348-356.

28. Le Heuzey JY, Paziaud O, Piot O, Said MA, Copie X, Lavergne T et al. Cost of care distribution in atrial fibrillation patients: the COCAF study. *Am Heart J* 2004; 147(1):121-126.

29. Stewart S, Murphy NF, Walker A, McGuire A, McMurray JJ. Cost of an emerging epidemic: an economic analysis of atrial fibrillation in the UK. *Heart* 2004; 90(3):286-292.

30. Wolf PA et al. Impact of atrial fibrillation on mortality, stroke, and medical costs. *Arch Intern Med* 1998; 158: 229–34.

31. Benjamin EJ, Chen PS, Bild DE, Mascette AM, Albert CM, Alonso A et al. Prevention of atrial fibrillation: report from a national heart, lung, and blood institute workshop. *Circulation* 2009; 119(4): 606-618.

32. Healey JS, Parkash R, Pollak T, Tsang T, Dorian P; CCS Atrial Fibrillation Guidelines Committee. Canadian Cardiovascular Society atrial fibrillation guidelines 2010: etiology and initial investigations. *Can J Cardiol* 2011; 27: 31-7.

33. Camm AJ, Kirchhof P, Lip GY, Schotten U, Savelieva I, Ernst S et al. Guidelines for the management of atrial fibrillation: The Task Force for the Management of Atrial Fibrillation of the European Society of Cardiology (ESC). *Eur Heart J* 2010; 31(19): 2369-429.

34. Major outcomes in high-risk hypertensive patients randomized to angiotensin-converting enzyme inhibitor or calcium channel blocker vs diuretic: The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). *JAMA* 2002; 288(23): 2981-2997.

35. Haywood LJ, Ford CE, Crow RS, et al. Atrial fibrillation at baseline and during follow-up in ALLHAT (Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial). *J Am Coll Cardiol* 2009; 54(22): 2023-31.

36. Lau DH, Mackenzie L, Kelly DJ, Psaltis PJ, Brooks AG, Worthington M et al. Hypertension and atrial fibrillation: Evidence of progressive atrial remodeling with electrostructural

correlate in a conscious chronically instrumented ovine model. *Heart Rhythm* 2010; 7(9): 1282-1290.

37. Johansen H, Strauss B, Arnold JM, Moe G, Liu P. On the rise: The current and projected future burden of congestive heart failure hospitalization in Canada. *Can J Cardiol* 2003; 19(4): 430-5.

38. Owan TE, Hodge DO, Herges RM, Jacobsen SJ, Roger VL, Redfield MM. Trends in prevalence and outcome of heart failure with preserved ejection fraction. *N Engl J Med* 2006; 355(3): 251-9.

39. Bursi F, Weston SA, Redfield MM. Systolic and diastolic heart failure in the community. *JAMA* 2006; 296(18): 2209-16.

40. Gheorghiade M, Colucci WS, Swedberg K. Beta-blockers in chronic heart failure. *Circulation* 2003; 107(12): 1570-5.

41. Klein L, O'Connor CM, Gattis WA, et al. Pharmacologic therapy for patients with chronic heart failure and reduced systolic function: review of trials and practical considerations. *Am J Cardiol* 2003; 91(9A): 18F-40F

42. Bardy GH, Lee KL, Mark DB, et al. Amiodarone or an implantable cardioverter-defibrillator for congestive heart failure*. N Engl J Med* 2005; 352(3): 225-37.

43. Abraham WT. Cardiac resynchronization therapy. *Prog Cardiovasc Dis* 2006; 48(4): 232-8.

44. Roger VL, Weston SA, Redfield MM, et al. Trends in heart failure incidence and survival in a community-based population. *JAMA* 2004; 292(3): 344-50.

45. Curtis LH, Whellan DJ, Hammill BG, et al. Incidence and prevalence of heart failure in elderly. *Arch Intern Med* 2008; 168(4): 418-24.

46. Braunwald E. Shattuck lecture--cardiovascular medicine at the turn of the millennium: triumphs, concerns, and opportunities. *N Engl J Med* 1997; 337(19): 1360-9.

47. Ehrlich, J.R., S. Nattel, and S.H. Hohnloser, Atrial fibrillation and congestive heart failure: specific considerations at the intersection of two common and important cardiac disease sets. J Cardiovasc Electrophysiol, 2002. 13(4): p. 399-405.

48. Cleland, J.G., et al., The EuroHeart Failure survey programme-- a survey on the quality of care among patients with heart failure in Europe. Part 1: patient characteristics and diagnosis. Eur Heart J, 2003. 24(5): p. 442-63.

49. Nieuwlaat, R., et al., Atrial fibrillation management: a prospective survey in ESC member countries: the Euro Heart Survey on Atrial Fibrillation. Eur Heart J, 2005. 26(22): p. 2422-34.

50. Middlekauff, H.R., W.G. Stevenson, and L.W. Stevenson, *Prognostic significance of atrial fibrillation in advanced heart failure. A study of 390 patients.* Circulation, 1991. 84(1): p. 40-8.

51. Dries, D.L., et al., *Atrial fibrillation is associated with an increased risk for mortality and heart failure progression in patients with asymptomatic and symptomatic left ventricular systolic dysfunction: a retrospective analysis of the SOLVD trials. Studies of Left Ventricular Dysfunction.* J Am Coll Cardiol, 1998. 32(3): p. 695-703.

52. Swedberg, K., et al., *Prognostic relevance of atrial fibrillation in patients with chronic heart failure on long-term treatment with beta-blockers: results from COMET.* Eur Heart J, 2005. 26(13): p. 1303-8.

53. Olsson, L.G., et al., *Atrial fibrillation and risk of clinical events in chronic heart failure with and without left ventricular systolic dysfunction: results from the Candesartan in Heart failure-Assessment of Reduction in Mortality and morbidity (CHARM) program.* J Am Coll Cardiol, 2006. 47(10): p. 1997-2004.

54. Wang, T.J., et al., *Temporal relations of atrial fibrillation and congestive heart failure and their joint influence on mortality: the Framingham Heart Study.* Circulation, 2003. 107(23): p. 2920-5.

55. Mamas, M.A., et al., *A meta-analysis of the prognostic significance of atrial fibrillation in chronic heart failure.* Eur J Heart Fail, 2009. **11**(7): p. 676-83.

56. Murray, S., Lazure, P., Pullen, C., et al. Atrial Fibrillation Care: Challenges in Clinical Practice and Educational Needs Assessment. *Can J Cardiol* 2011; 27:98-104.

57. Lindsay MP, Gubitz G, Baylet M, Phillips S (Editors) on Behalf of the Canadian Stroke Best Practices and Standards Working Group. Canadian Best Practice Recommendations for Stroke Care, Fourth Edition. 2012. http://www.strokebestpractices.ca/wp-content/uploads/2012/10/20120BPR_Ch2_Prevention_Final-Version_20Sept-2012F-12.pdf

58. Simpson CS, Healey JS, Philippon F, Dorian P, Mitchell LB, Sapp JL, Jr. et al. Universal access -- but when? Treating the right patient at the right time: access to electrophysiology services in Canada. *Can J Cardiol* 2006; 22(9):741-746.

59. Wyse DG, Waldo AL, DiMarco JP, Domanski MJ, Rosenberg Y, Schron EB et al. A comparison of rate control and rhythm control in patients with atrial fibrillation. *N Engl J Med* 2002; 347(23): 1825-1833.

60. Corley SD, Epstein AE, DiMarco JP, Domanski MJ, Geller N, Greene HL et al. Relationships between sinus rhythm, treatment, and survival in the Atrial Fibrillation Follow-Up Investigation of Rhythm Management (AFFIRM) Study. *Circulation* 2004; 109(12): 1509-1513.

61. Vidaillet HJ. Rate control vs. rhythm control in the management of atrial fibrillation in elderly persons. *Am J Geriatr Cardiol* 2005; 14(2): 73-8.

62. Evers T, O'Neil W, Ogilvie I et al. Stroke prevention in patients with atrial fibrillation: Inappropriate anticoagulation and poor INR control. 2011. ISPOR Conference, Madrid Spain. http://www.biomedcom.org/docs/2011/Evers2011ISPORPosterPresentation1.pdf

63. Samsa GP, et al. *Arch Intern Med* 2000; 160: 967-973

64. Haissaguerre M, Jais P, Shah DC, Takahashi A, Hocini M, Quiniou G et al. Spontaneous initiation of atrial fibrillation by ectopic beats originating in the pulmonary veins. *N Engl J Med* 1998; 339(10):659-666.

65. Cappato R, Calkins H, Chen SA, Davies W, Iesaka Y, Kalman J et al. Worldwide survey on the methods, efficacy, and safety of catheter ablation for human atrial fibrillation. *Circulation* 2005; 111(9):1100-1105.

66. Verma A, MacLe L, Cox J, Skanes AC. Canadian cardiovascular society atrial fibrillation guidelines 2010: catheter ablation for atrial fibrillation/atrial flutter. *Can J Cardiol* 2011; 27(1):60-66.

67. Assasi N, Blackhouse G, Xie F, Gaebel K, Robertson D, Hopkins R, Healey J, Roy D, Goeree R. Ablation procedures for rhythm control in patients with atrial fibrillation: clinical and cost-effectiveness analyses [Internet]. Ottawa: Canadian Agency for Drugs and Technologies in Health; 2010 (Technology report; no. 128). Available from: http://www.cadth.ca/index.php/en/hta/reports-publications/search?&type=16.

68. Hohnloser SH, Crijns HJ, van EM, Gaudin C, Page RL, Torp-Pedersen C et al. Effect of dronedarone on cardiovascular events in atrial fibrillation. *N Engl J Med* 2009; 360(7):668-678.

69. Berg J, Sauriol L, Lindgren P. Canadian cost-effectiveness analysis of dronedarone in patients with atrial fibrillation based on the ATHENA trial. Poster presented at the European Society of Cardiology Congress 2010, Stockholm, August 2010. Available at: spo.escardio.org/eslides/view.aspx?eevtid=40&fp=P1444; accessed June 8, 2011.

70. Nilsson J, Akerborg O, Bascle S, Sauriol L, Lindgren P. Canadian cost-effectiveness analysis of dronedarone versus other anti-arrhythmic drugs in patients with paroxysmal and persistent atrial fibrillation. Poster presented at the International Society for Pharmaco-

economics and Outcomes Research 13th Annual European Congress, Prague, November 2010.

71. D. Wayne Taylor, The mad, mad world of Pharmacare in Canada: access to newer treatments for atrial fibrillation. *The Cameron Institute*. December 2010. Available at: cameroninstitute.com/.../048_Access%20to%20newer%20treatments%20for%20AF.pdf; accessed on June 8, 2011.

72. Maund E, McKenna C, Sarowar M, Fox D, Stevenson M, Pepper C, Palmer S, Woolacott N. Dronedarone for the treatment of atrial fibrillation and atrial flutter. *Health Technol Assess* 2010; 14(Suppl. 2): 55-62.

73. Corman SL, Smith K. Cost-effectiveness of dronedarone compared to amiodarone for patients with paroxysmal atrial fibrillation. Poster presented at the 32nd Annual Meeting of the Society for Medical Decision Making. Toronto, ON, Canada, October 2010. Available at: http://smdm.confex.com/smdm/2010on/webprogram/Paper5136.html; accessed June 8, 2011.

74. Cadet JV. HRS: AF and atrial flutter remain large cost burden in U.S. May 12, 2011, Cardiovascular Business. http://www.cardiovascularbusiness.com/index.php?option=com_conferences&article=27722&conference=24&event=&topic=1673&form=article27722&limitstart=80.

75. Mega JL. A new era for anticoagulation in atrial fibrillation. N Engl J Med. 2011; 365: 1052–1054.

76. Skanes et al., and the Canadian Cardiovascular Society Atrial Fibrillation Guidelines Committee. Focused update of the Canadian Cardiovascular Society atrial fibrillation guidelines: updated recommendations for stroke prevention and rate/rhythm control. *Can J Cardiol* 2012; 28: 125–136.

77. Connolly SJ, Ezekowitz MD, Yusuf S, Eikelboom J, Oldgren J, Parekh A, et al; RE-LY Advisory Committee and Investigators. Dabigatran versus warfarin in patients with atrial fibrillation. *N Engl J Med.* 2009; 361: 1139–1151

78. Patel MR, Mahaffey KW, Garg J, Pan G, Singer DE, Hacke W, et al; ROCKET AF Investigators. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. *N Engl J Med.* 2011; 365: 883–891

79. Granger CB, Alexander JH, McMurray JJ, Lopes RD, Hylek EM, Hanna M, et al; ARISTOTLE Committees and Investigators. Apixaban versus warfarin in patients with atrial fibrillation. *N Engl J Med.* 2011; 365: 981–992

80. Gillis AM, Burland L, Arnburg B, Kmet C, Pollak PT, Kavanagh K et al. Treating the right patient at the right time: an innovative approach to the management of atrial fibrillation. *Can J Cardiol* 2008; 24(3):195-198.

81. Jeroen M. Hendriks, Rianne de Wit, Harry J. Crijns, Hubertus J. Vrijhoef, Martin H. Prins, Ron Pisters, Laurent A. Pison, Yuri Blaauw, Robert G. Specialised Atrial Fibrillation Clinic Reduces Cardiovascular Morbidity and Mortality in Patients with Atrial Fibrillation — Tieleman, Maastricht University Medical Centre, Maastricht, The Netherlands. Featured Clinical Research. ACC/i2 Joint Session (oral presentation), Tuesday, April 5, 2011. American College of Cardiology Scientific Sessions 2011. See: http://cardioletter.org/index.tpl?rubrik=165; accessed June 8, 2011.

82. Ducharme A, Doyon O, White M, Rouleau JL, Brophy JM. Impact of care at a multidisciplinary congestive heart failure clinic: a randomized trial. *CMAJ* 2005; 173(1):40-45.

83. McAlister FA, Stewart S, Ferrua S, McMurray JJ. Multidisciplinary strategies for the management of heart failure patients at high risk for admission: a systematic review of randomized trials. *J Am Coll Cardiol* 2004; 44: 810-9.

84. Howlett JG, Mann OE, Baillie R, Hatheway R, Svendsen A, Benoit R, Ferguson C, Wheatley M, Johnstone DE, Cox JL. Heart failure clinics are associated with clinical benefit in both tertiary and community care settings: data from the Improving Cardiovascular Outcomes in Nova Scotia (ICONS) registry. *Can J Cardiol* 2009; 25: e306-11

85. Wijeysundera HC, Machado M, Wang X, Van D, V, Sikich N, Witteman W et al. Cost-effectiveness of specialized multidisciplinary heart failure clinics in Ontario, Canada. *Value Health* 2010; 13(8):915-921.

86. Arnold, JMO; Howlett, JG; Dorian, P; Ducharme, A; Ezekowitz, JA; Gardner, MJ; Giannetti, N; Haddad, H; Heckman, GA; Isaac, D; JLong, P; Liu, P, Mann, E; McKelvie, RS; Moe, GW; Svendsen, AM; Tsuyuki, T; O'Halloran, K; Ross, HJ; Sequera, EJ; White,M. Canadian Cardiovascular Society Consensus Conference guidelines on heart failure - 2008 update: Best practices for the transition of care of heart failure patients, and the recognition, investigation and treatment of cardiomyopathies. *Can J Cardiol* 2008; 24: 21-40.

87. Hauptman PJ, Rich MW, Heidenreich PA, Chin J, Cummings N, Dunlap ME, Edwards ML, Gregory D, O'connor CM, Pezzella SM, Philbin E; Heart Failure Society of America. The heart failure clinic: a consensus statement of the Heart Failure Society of America. *J Card Fail* 2008; 14: 801-15.

88. Ron Pisters, Robby Nieuwlaat, Cees B. de Vos, and Harry J. Crijns. Comprehensive upstream treatment for atrial fibrillation, when and how? *Europace* 2009; 11: 397–399.

89. Gross PA, Patriaco D, McGuire K, Skurnick J, Teichholz LE. A nurse practitioner intervention model to maximize efficient use of telemetry resources. *Jt Comm J Qual Improv* 2002; 28(10): 566-573.

90. Shelton RJ, Allinson A, Johnson T, Smales C, Kaye GC. Four years experience of a nurse-led elective cardioversion service within a district general hospital setting. *Europace* 2006; 8(1): 81-85.

91. Boodhoo L, Bordoli G, Mitchell AR, Lloyd G, Sulke N, Patel N. The safety and effectiveness of a nurse led cardioversion service under sedation. *Heart* 2004; 90(12): 1443-1446.

92. Andersen MK, Markenvard JD, Schjott H, Nielsen HL, Gustafsson F. Effects of a nurse-based heart failure clinic on drug utilization and admissions in a community hospital setting. *Scand Cardiovasc J* 2005; 39(4): 199-205.

93. Andersson B, Kjork E, Brunlof G. Temporal improvement in heart failure survival related to the use of a nurse-directed clinic and recommended pharmacological treatment. *Int J Cardiol* 2005; 104(3): 257-263.

94. IOM (Institute of Medicine). *Initial National Priorities for Comparative Effectiveness Research.* Washington, DC: The National Academies Press, 2009. Available at: www.tuftsctsi.org/~/media/.../IOM%20on%20CER%20063009.ashx; accessed on June 8, 2011.

95. http://www.statcan.gc.ca/ig-gi/pop-ns-eng.htm; accessed May 12, 2011.

96. Public Health Agency of Canada, *2009 Tracking Heart Disease and Stroke in Canada*. Available at: http://www.phac-aspc.gc.ca/publicat/2009/cvd-avc/index-eng.php; accessed April 19, 2010.

97. Statistics Canada. 2010. Visual census. 2006 Census. Ottawa. Released December 7, 2010. http://www12.statcan.gc.ca/census-recensement/2006/dp-pd/fs-fi/index.cfm?Lang=ENG&TOPIC_ID=7&PRCODE=12 (accessed August 08, 2013).

98. Statistics Canada. 2010. Visual census. 2006 Census. Ottawa. Released December 7, 2010. http://www12.statcan.gc.ca/census-recensement/2006/dp-pd/fs-fi/index.cfm?Lang=ENG&TOPIC_ID=11&PRCODE=12 (accessed August 08, 2013)

99. http://www.chhs.ca/en/reports.

100. http://www.nshrf.ca/initiatives/initiatives/health-research-priorities.

101. Cox JL, on behalf of the ICONS Investigators. Optimizing disease management at a health care system level: the rationale and methods of the Improving Cardiovascular Outcomes in Nova Scotia (ICONS) Study. *Can J Cardiol* 1999; 15: 787-96.

102. Cox JL, O'Neill BJ, Vallis TM, Carr B, Szpilfogel C. A Novel Approach To Cardiovascular Health By Optimizing Risk Management (ANCHOR): A primary prevention initiative examining the impact of global risk factor assessment & management on health care. *Can J Cardiol* 2011; (6): 809-17.

103. Montague T, Cox J, Kramer S, Nemis-White J, Cochrane B, Wheatley M, Joshi Y, Carrier R, Gregoire J-P, Johnstone D, for the ICONS investigators. Improving cardiovascular outcomes in Nova Scotia: ICONS, a successful public/private partnership in primary health care. *Hospital Quarterly* 2003; 6: 32-8.

104. Cox J, Johnstone D, Nemis-White J, Montague T, for the ICONS Investigators. Optimizing health care at the population level: Results of the improving cardiaovascular outcomes in Nova Scotia (ICONS) partnership. *Healthcare Quarterly* 2008; 11 (2): 28-41.

105. Crémieux P-Y, Fortin P, Meilleur MC, Montague T, Royer J. The economic impact of a partnership-measurement model of disease management: Improving cardiovascular outcomes in Nova Scotia (ICONS). *Healthcare Quarterly* 2007; 10: 36-44.

106. Paradis PE, Nemis-White J, Meilleur M-C, Ginn M, Cox J, Montague T, for the Improving Cardiovascular Outcomes in Nova Scotia (ICONS) Investigators. Managing Care and Costs: The sustained cost impact of reduced hospitalizations in a partnership-measurement model of disease management. *Healthcare Quarterly* 2010; 13(4): 30-39.

107. Hohnloser SH, Connolly SJ, Crijns HJ, et al. Rationale and design of ATHENA. *J Cardiovasc Electrophysiol* 2008 19:1;69-73.

108. Schulman S, Kearon C. Definition of major bleeding in clinical investigations of antihemostatic medicinal products in non-surgical patients. *J Throm Haem* 2004; 3:692-694

109. Tunis SR, Stryer DB, Clancy CM. Practical clinical trials: increasing the value of clinical research for decision making in clinical and health policy. *JAMA* 2003; 290: 1624-1632.

110. Ware JH, Hamel MB. Pragmatic trials – guides to better patient care? *N Engl J Med* 2011; 364: 1685-1687.

111. McMahon AD. Study control, violators, inclusion criteria and defining explanatory and pragmatic trials. *Statist Med* 2002; 21: 1365-1376.

112. Singer N. 2010. Better Health, with a Little Help from Our Friends. *New York Times*, 18 September.

113. Centola D. 2010. The Spread of Behavior in an Online Social Network Experiment *SCIENCE;* 329: 1194-7.

114. Ehrlich, J.R., Nattel, S., & Hohnloser, S.H. (2002). Atrial Fibrillation and Congestive Heart Failure: Specific Considerations at the Intersection of Two Common and Important Cardiac Disease Sets. Journal of Cardiovascular Electrophysiology, 13(4): 399-405.

115. Wang, D., Peleg, M., Tu, S. W., Boxwala, A., Greenes, R., Patel, V.L., et al. (2002). Representation primitives, process models and patient data in computer-interpretable clinical guidelines: A literature review of guideline representation models. International Journal of Medical Informatics, 68: 59-70

116. Tu. S.W., Musen, M.A., Shankar, R., Campbell, J., Hrabak, K., McClay, J. et al. (2004). Modeling Guidelines for Integration into Clinical Workflow. Proceedings of 11th World Congress on Medical Informatics (pp 174-178). Amsterdam: IOS Press

117. W3C-OWL Web Ontology Language Overview. Retrieved Oct. 4th 2012 from http://www.w3.org/TR/2004/REC-owl-features-20040210/#s1.2

118. Hussain, S., SSR ABIDI. K-Morph: A Semantic Web Based Knowledge Representation and Context-driven Morphing Framework. Workshop on Context and Ontologies at 18th European Conference on Artificial Intelligence (ECAI2008), Patras (Greece), July, 2008.

119. Boxwala, A.A., Peleg, M., Tu, S., Oqunyemi, O., Zeng, Q.T., Wang, D. et al. (2004). GLIF3: a representation format for sharable computer-interpretable clinical practice guidelines. J Biomed Inform, 37(3): 147-61

120. Sutton, D.R & Fox, J. (2003). The syntax and semantics of the PROforma guideline modeling language. J Am Med Inform, 10(5): 433–443

121. Fensel, D., & Musen, M.A, (2001). The Semantic Web: A Brain for Humankind. IEEE Intelligent Systems, 16(2): 24-25

122. Assessing risk of bias in cluster-randomized trials. http://www.mrc-bsu.cam.ac.uk/cochrane/handbook/chapter_16/16_3_2_assessing_risk_of_bias_in_cluster_randomized_trials.htm

123. http://www.srpc.ca/resources_regional_stats.html

124. Brauer CA, Rosen AB, Greenberg D, Neumann PJ. Trends in the measurement of health utilities in published cost-utility analyses. *Value Health* 2006;9:213-218

125. Brooks R. EuroQol: the current state of play. *Health Policy* 1996;37:53-72

126. Herdman M, Gudex C, Lloyd A et al. Development and preliminary testing of the new five-level version of EQ-5D (EQ-5D-5L). *Qual Life Res* 2011;20:1727-1736.

127. Camm A.J., Breithardt, G., Crijns, H., et al. Real-Life Observations of Clinical Outcomes with Rhythm- and Rate-Control Therapies for Atrial Fibrillation. JACC 2011. 58(5):493-501.

128. Dregan A., Toschke M., Wolfe C. et al. Utility of electronic patient records in primary care for stroke secondary prevention trials. BMC Public Health 2011, 11:86

129. www.consort-statement.org

130. Hardin JW, Hilbe JM. Generalized estimating equations. Chapman & Hall/CRC: New York, NY 2002.

131. Ma J et al. Comparison of Bayesian and classical methods in the analysis of cluster randomized controlled trials with a binary outcome: the Community Hypertension Assessment Trial (CHAT). BMC Medical Research Methodology 2009; 9: 37.

132. Hendricks JML, de Wit R, Crijns HJGM et al. Nurse-led care vs. usual care for patients with atrial fibrillation: Results of a randomized trial of integrated chronic care vs. routine clinical care in ambulatory patients with atrial fibrillation. Eur Heart J 2012; 2692-2699.

133. Rubin, DB. Multiple Imputation for Nonresponse in Surveys. 1987. New York; John Wiley & Sons, Inc.

9.0 APPENDIX

9.1. Project Organogram