A Randomized **A**blation-based atrial **F**ibrillation rhythm control versus rate control **T**rial in patients with heart failure and high burden **A**trial **F**ibrillation
The **RAFT-AF** Trial

NCT01420393

Study Protocol

Version 7.2

Dated December 18, 2020

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SPONSOR:

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Investigator Agreement

"I have read this protocol and agree to abide by all provisions set forth therein.
I agree to comply with the International Conference on Harmonisation Tripartite Guideline on Good Clinical Practice."

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Co-Investigator (Print Name)	Investigator Signature	Date DD/MMM/YYYY
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LIST OF ABBREVIATIONS

6MW	6-minute Walk Test
ACEI	Angiotensin Converting Enzyme Inhibitors
AE	Adverse Event
AF	Atrial Fibrillation
ARB	Angiotensin II Receptor Blockers
ASD	Atrial Septal Defect
AVN	Atrioventricular Nodal
BPM	Beats per Minute
CRF	Case Report Form
CRMC	Cardiovascular Research Method Centre
CRT	Cardiac Resynchronization Therapy
CT	Computed Tomography
CV	Cardiovascular
DMC	Data Monitoring Committee
ECG	Electrocardiogram
ICF	Informed Consent Form
IRB	Institutional Review Board
ITT	Intent-to-treat
H_x	Medical History
HF	Heart Failure
HR	Heart Rate
LA	Left Atrium
LV	Left Ventricular
LVEF	Left Ventricular ejection fraction
MCID	Minimal Clinically Important Difference
MR	Cardiac Magnetic Resonance
N	Number (typically refers to patients)
Approved OAC	Approved Oral Anticoagulants
NSR	Normal Sinus Rhythm
NT-proBNP	Amino terminal pro brain natriuretic peptide
NYHA	New York Heart Association
OHI	Ottawa Heart Institute
PI	Principal Investigator
PVI	Pulmonary Vein Isolation
PROBE	Prospective Randomized Open Blinded Endpoint Trial
QOL	Quality of life
RAFT	Resynchronization-defibrillation in Ambulatory Heart Failure Trial
REB	Research Ethics Board
RRR	Relative Risk Reduction
SAE	Serious Adverse Event
US	United States

PROTOCOL SUMMARY

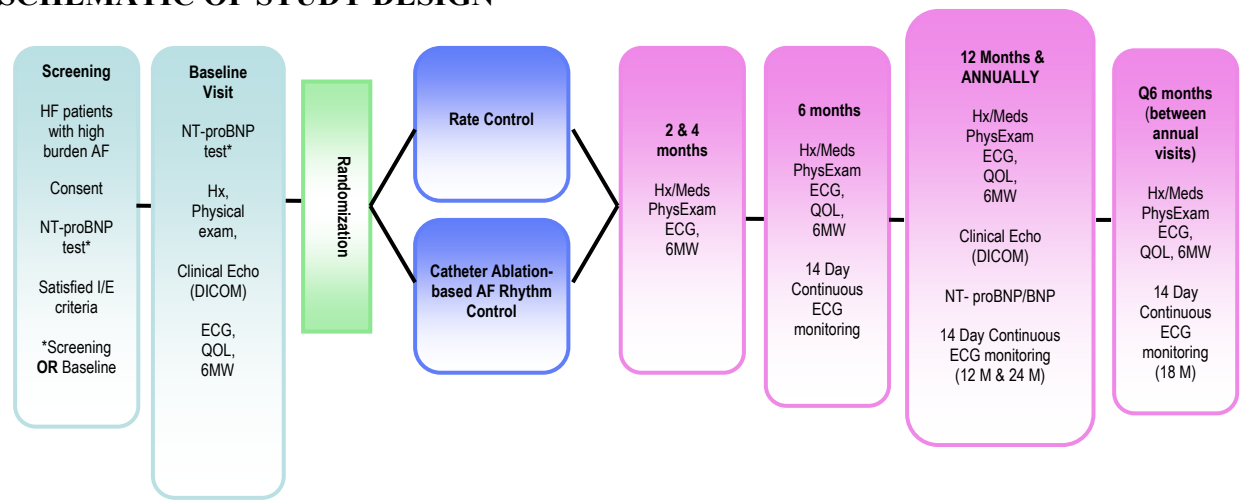
Full Title	**A R**andomized **A**blation-based atrial **F**ibrillation rhythm control versus rate control **T**rial in patients with heart failure and high burden **A**trial **F**ibrillation
Short Title	The **RAFT-AF** Trial
Clinical Phase	Phase 4
Sponsor	Ottawa Heart Institute Research Corporation (OHIRC)
Conducted By	Cardiovascular Research Method Centre (CRMC) at the University of Ottawa Heart Institute
Principal Investigator	Dr. Anthony Tang
Primary Objectives	In patients with HF (either impaired (LVEF≤45%) or preserved (LVEF > 45%) and high burden AF, to determine if catheter ablation-based rhythm control of AF, as compared with rate control, will reduce all-cause mortality and heart failure event defined as an admission to a healthcare facility for > 24 hours or clinically significant worsening heart failure leading to an intervention (defined as treatment in an emergency department, a same-day access clinic, or an infusion centre) or unscheduled visits to a healthcare provider for administration of an intravenous diuretic as accepted by FDA, and an increase in chronic heart failure therapy (see definition Appendix O, June 2019)
Secondary Objectives	In patients with HF (either impaired (LVEF≤45%) or preserved (LVEF > 45%) and high burden AF, to determine if catheter ablation-based rhythm control of AF, as compared with rate control will: A. Reduce all-cause mortality B. Reduce heart failure event * C. Improve QOL (as determined by MLWF, EQ5D and AFEQT questionnaires) D. Improve exercise capacity (as determined by 6 Minute Hall walk distance) E. Reduce NT-proBNP at 1 year and at 2 year follow-up** F. In patients with HF, impaired (LVEF ≤ 45%) LV function and high burden AF, to determine if catheter ablation-based rhythm control of AF, as compared with rate control, will reduce all-cause mortality and heart failure event* G. In patients with HF, preserved (LVEF > 45%) LV function and high burden AF, to determine if catheter ablation-based rhythm control of AF as compared with rate control will reduce all-cause mortality and heart failure events* H. Be more cost effective ** Heart failure event defined as an admission to a healthcare facility for > 24 hours or clinically significant worsening heart failure leading to an intervention (defined as treatment in an emergency department, a same-day access clinic, or*

	an infusion centre) or unscheduled visits to a healthcare provider for administration of an intravenous diuretic as accepted by FDA and an increase in chronic heart failure therapy (see definition in Appendix O, June 2019) *** In a subset of sites in Canada: NT-proBNP (BNP) values, Echocardiogram measures of LV function, AF Burden (14 day Continuous ECG Monitoring)*
Tertiary Objectives	In patients with HF (either impaired (LVEF≤45%) or preserved (LVEF > 45%) LV function) and high burden AF, to determine if catheter ablation-based rhythm control of AF, as compared with rate control will: A. Improve LV function and remodeling (LVESVI) at 1 year and 2 year follow-up** B. Reduce AF burden at 1 year and 2 year follow-up** C. Reduce the total number of heart failure events* D. Decrease the total number of CV hospitalization (including AV node ablation, device admissions) ** Heart failure event (defined as an admission to a healthcare facility for > 24 hours or clinically significant worsening heart failure leading to an intervention (defined as treatment in an emergency department, a same-day access clinic, or an infusion centre) or unscheduled visits to a healthcare provider for administration of an intravenous diuretic as accepted by FDA and an increase in chronic heart failure therapy (see definition in Appendix O, June 2019)* *** In a subset of sites in Canada: NT-proBNP (BNP) values, Echocardiogram measures of LV function, AF Burden (14 day Continuous ECG Monitoring)*
Safety Objectives	In patients with HF (either impaired (LVEF≤45%) or preserved (LVEF > 45%) LV function and high burden AF, to determine if catheter ablation-based rhythm control of AF, as compared with rate control, will not increase adverse events including thromboembolic events, symptomatic PV stenosis, atrio-esophageal fistula, pericardial effusion requiring pericardiocentesis, major bleeding requiring blood transfusion, amiodarone induced thyroid, pulmonary and other toxicity
Study Population	Adults (≥18yrs) with NYHA class II-III HF, either impaired LV (LVEF ≤45%) or preserved LV (LVEF >45%), high burden AF (frequent paroxysmal, persistent and long-term persistent) and NT-pro BNP measures: **A)** Patient has been hospitalized for Heart Failure* in the past 9 months, has been discharged AND: i- Is presently in Normal Sinus Rhythm and NT-pro BNP is ≥ 400 pg/mL ii- Is presently in Atrial Fibrillation and NT-pro BNP is ≥ 600 pg/mL **OR** **B)** Patient has had no hospitalization for Heart Failure in the past 9 months AND: i- Has had paroxysmal Atrial Fibrillation, is presently in Normal Sinus Rhythm and NT-proBNP is ≥ 600 pg/mL ii- Is presently in Atrial Fibrillation and NT-proBNP is ≥ 900 pg/mL

	*Heart Failure Admission is defined as admission to hospital > 24 hours and received treatment for Heart failure
Study Design	A multi-centre prospective randomized open study with blinded endpoint assessment (PROBE design). Patients will be randomized to either rate control or catheter ablation-based AF rhythm control in a 1:1 randomization ratio
Sample Size	N = 600 patients, from over 30 recruitment centres
Accrual Period	3 years
Study Duration	Start Date: December 2011 End Date: February 2020 Maximum 9 years: minimum follow-up for each patient will be 24 months
Outcome Measures	Primary Endpoint: Composite of all-cause mortality and heart failure event* Secondary Endpoints: All-cause mortality, heart failure event*, QOL (as determined by MLWF, EQ5D and AFEQT questionnaires), Exercise capacity (6 Minute hall walk), NT-proBNP at 1 & 2 Year follow up**, In patients with HF, impaired (LVEF≤45%) LV function and high burden AF, all-cause mortality and heart failure event*, In patients with HF, preserved (LVEF > 45%) LV function and high burden AF, all-cause mortality and heart failure event* and Cost effectiveness Safety Endpoints: In patients with HF (either impaired (LVEF≤45%) or preserved (LVEF > 45%) LV function) and high burden AF, to determine if catheter ablation-based rhythm control of AF, as compared with rate control, will not increase adverse events including thromboembolic events, symptomatic PV stenosis, atrio-esophageal fistula, pericardial effusion requiring pericardiocentesis, major bleeding requiring blood transfusion, amiodarone induced thyroid, pulmonary and other toxicity ** Heart failure event defined as an admission to a healthcare facility for > 24 hours or clinically significant worsening heart failure leading to an intervention (defined as treatment in an emergency department, a same-day access clinic, or an infusion centre) or unscheduled visits to a healthcare provider for administration of an intravenous diuretic as accepted by FDA and an increase in chronic heart failure therapy (see definition in Appendix O, June 2019)* *** In a subset of sites in Canada: NT-proBNP (BNP) values, Echocardiogram measures of LV function, AF Burden (14 day Continuous ECG Monitoring)*
Study Description	Patients will be randomized to either rate control or catheter ablation-based AF rhythm control in a 1:1 randomization ratio. Patients in the rate control group will receive optimal HF therapy and rate control measures to achieve a resting HR < 80 bpm and 6-minute walk HR < 110 bpm. Patients randomized to catheter ablation-based AF rhythm control group will receive optimal HF

	therapy and one or more aggressive catheter ablation, which include PV antral ablation and LA substrate ablation with or without adjunctive antiarrhythmic drug. Patients will be followed regularly and will have clinical evaluation, quality of life assessment and 6-minute walk test.

SCHEMATIC OF STUDY DESIGN



STUDY SYNOPSIS

***Background*:** Heart failure (HF) and atrial fibrillation (AF) are two cardiac conditions that are increasing in prevalence and incidence. Both are associated with increased mortality and morbidity. The two conditions frequently co-exist and are associated with even higher deaths and suffering. Pathophysiologically, one condition potentiates the other, causing a downward spiral. The management of AF, in patients with HF, is challenging. It seems intuitive that abolishing AF may break the vicious circle and should be beneficial. However, previous studies using antiarrhythmic drug-based rhythm control, have not shown any mortality benefit over rate control. This may be that AF is just a marker of more advanced disease progression, or that the method of rhythm control is not adequate, or that the population studied is not appropriate. This trial addresses the latter two possibilities. Catheter ablation has become a standard therapy for patients with drug-resistant AF. This therapy has been shown to be effective, cost-effective and a reasonably safe procedure, with the ability to offer a higher rhythm control rate than antiarrhythmic drugs. Catheter ablation of AF has been successfully performed in patients with HF, with an improvement of surrogate outcome measures: increased left ventricular (LV) ejection fraction, better quality of life (QOL), reduced NT-proBNP, but there is no large scale, long term data to show this approach affects mortality.

Objectives: The primary objective is to determine if AF is an instigator or a marker of adverse clinical outcomes and whether vigorous rhythm treatment of AF by aggressive catheter ablation treatment, with or without antiarrhythmic drugs will reduce all-cause mortality and heart failure events*[99] as compared with rate control in patients with HF (either impaired (LVEF≤45%) or preserved (LVEF > 45%) LV function and high burden AF. The secondary objectives are to determine in patients with HF (either impaired (LVEF≤45%) or preserved (LVEF > 45%) LV function) and high burden AF: 1) Reduce all-cause mortality 2) Reduce HF events, 3) Improve QoL 4) Improve exercise capacity (6 minute hall walk); 5) Reduce NT-proBNP at 1 & 2 year; 6 & 7) In patients with HF, impaired (LVEF≤45%) or preserved (LVEF > 45%) LV function and high burden AF, to determine if catheter ablation-based rhythm control of AF, as compared with rate control, will reduce all-cause mortality and heart failure events*; & 8)Be more cost-effective

***Methods*:** This is a multi-centre prospective randomized open study with blinded endpoint assessment (PROBE design). Patients with NYHA class II-III HF (impaired (LVEF≤45%) LV or preserved (LVEF > 45%) LV), the patient has been hospitalized for Heart Failure in the past 9 months and NT-proBNP ≥ 400 pg/mL if in NSR or ≥ 600 pg/mL if in AF **OR** the patient has had no admissions for HF in the past 9 months and has had atrial fibrillation, is presently in NSR and the NT-proBNP ≥ 600 pg/mL or is presently in atrial fibrillation and NT-proBNP is ≥ 900 pg/mL and high burden AF (frequent paroxysmal, persistent and long-term persistent) will be included in the trial. Patients will be randomized to either rate control or catheter ablation-based AF rhythm control in a 1:1 randomization ratio. Patients in the rate control group will receive optimal HF therapy and rate control measures to achieve a resting HR < 80 bpm and 6-minute walk HR < 110 bpm. Patients randomized to catheter ablation-based AF rhythm control group will receive optimal HF therapy and one or more aggressive catheter ablation, which include PV antral ablation and LA substrate ablation with or without adjunctive antiarrhythmic drug. Patients will be followed regularly and will have clinical evaluation, quality of life assessment and 6-minute walk test. The primary outcome is a composite of all-cause mortality and heart failure event*. Secondary outcomes will include 1) Reduce all-cause mortality 2) Reduce HF events*, 3) Improve QOL (as determined by MLWF, EQ5D and AFEQT questionnaires) 4) Improve exercise capacity 5) Reduce NT-proBNP at 1 & 2 year**, 6 &7) In patients with HF, impaired (LVEF≤45%) or preserved (LVEF > 45%) LV function and high burden AF, to determine if catheter ablation-based rhythm control of AF, as compared with rate control, will reduce all-cause mortality and heart failure events* 8) Be more cost-effective. The event rate of the composite endpoint is estimated to be 17% per year. In order to detect a 30% relative risk reduction of the primary outcome at alpha=0.05 (two-sided) with 80% power, a sample size of no less than 600 patients will be required. There will be at least 30 centres participating. Patient accruement is scheduled for three years with a minimum follow-up of 24 months.

** defined as an admission to a healthcare facility for > 24 hours or clinically significant worsening heart failure leading to an intervention (defined as treatment in an emergency department, a same-day access clinic, or an infusion centre) or unscheduled visits to a healthcare provider for administration of an intravenous diuretic as accepted by FDA and an increase in chronic heart failure therapy (see definition in Appendix O, June 2019).*

*** In a subset of sites in Canada: NT-proBNP (BNP) values, Echocardiogram measures of LV function, AF Burden (14 day Continuous ECG Monitoring)*

1. INTRODUCTION: BACKGROUND INFORMATION and SCIENTIFIC RATIONALE

1.1.BACKGROUND INFORMATION

1.1.1. Atrial Fibrillation and Heart Failure

Heart failure (HF) is increasing in prevalence and incidence, affecting 5.8 million patients in the United States (US). The estimated direct and indirect cost of HF in the US for 2010 is $39.2 billion[1]. Similarly, HF in Canada is on the rise[2]. HF patients may have impaired (LVEF≤45%) or preserved (LVEF > 45%) left ventricular (LV) function in approximate equal proportions[3, 4]. Over the last 20 years there has been significant progress in the management of HF patients with impaired (LVEF≤45%) LV using beta-blockade[5], angiotensin converting enzyme inhibitors (ACEI), angiotensin II receptor blockers (ARB), aldosterone antagonist[6], implantable cardioverter-defibrillator (ICD)[7] and cardiac resynchronization therapy (CRT)[8]. In HF patients with preserved LV function, the treatment is symptom relief with diuretics and control of blood pressure. The survival rate improved over time among individuals with impaired (LVEF≤45%) LV, but not among those with preserved (LVEF>45%) LV[3]. The overall mortality and hospitalization rate remains high[9, 10].

Atrial fibrillation (AF) is a common cardiac arrhythmia affecting 1-2% of the population of the western world[11]. AF significantly impairs quality of life[12, 13] and accounts for >350,000 US hospital admissions annually[14]. It is associated with increased risk of stroke, and overall mortality in epidemiology studies. The Framingham heart study showed that AF was associated with a 1.5 to 1.9 fold mortality risk after adjustment for the preexisting cardiovascular (CV) conditions with which AF was related[15]. In the Marshfield epidemiology study, patients with AF had a 2.5 fold increased mortality risk[16]. This has also been observed in contemporary clinical trials. In an analysis of the hypertension trial, ALLHAT, baseline AF was associated with an increased mortality (hazard ratio = 2.82; 95% CI 2.36-3.37)[17].

AF and HF frequently co-exist[18]. The prevalence of AF increases in patients with more advanced HF symptoms[19]. The Euro Heart Surveys of current cardiology practice showed that HF is present in 34% of AF patients, and AF in 42% of HF patients [20, 21]. Mechanisms for AF and HF co-existing are: 1) AF with rapid ventricular response can lead to rate-related cardiomyopathy[22]; 2) The loss of atrial transport causes a fall in cardiac output[23]; 3) HF causes increased atrial filling pressure and atrial dilatation promoting AF by ionic remodeling and atrial fibrosis[24]; and 4) Atrial tissue stretch caused by HF promotes AF by inducing triggered activity, affecting atrial refractoriness[25]. Furthermore, treatment to relieve chronic stretch has been demonstrated to reverse the remodeling process[26-28]; and treatment to eliminate AF in patients with LV dysfunction improves LV function[29,30]. These data suggest that effective means to abolish AF may break the vicious circle and result in a better mortality and morbidity. *However, this has not been demonstrated and is the subject of this proposed study.*

1.1.2. Prognosis of patients with AF and HF

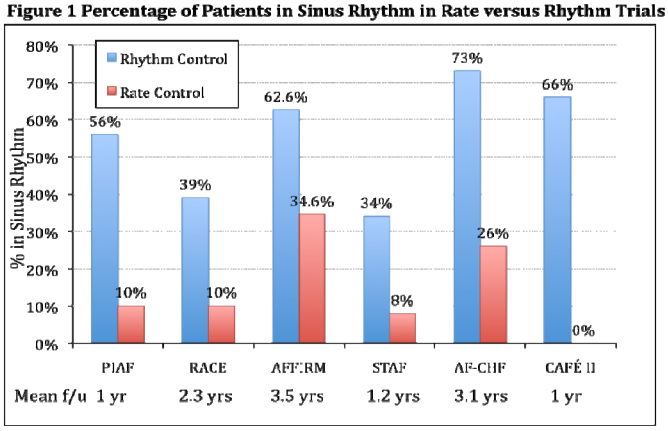
Clinical evidence, from population studies and clinical trials, suggests that HF patients with AF have a worse prognosis than without AF[31-35]. A recent meta-analysis, including 53,969 patients from 9 observational and 7 randomized trials, concluded that after adjusting for confounding factors, AF is associated with an increased total mortality with an odds ratio (OR) of 1.40 (95%

CI 1.32-1.48) in randomized trials and an OR of 1.14 (95% CI 1.03-1.26) in observational studies. Moreover, AF is associated with worse mortality in HF patients with impaired (LVEF≤45%) LV (OR 1.49), as well as in patients with preserved (LVEF > 45%) LV (OR 2.0)[36].

1.1.3. AF and HF Treatment Interactions

Pharmacological therapy to treat AF: The treatment of AF in HF patients is challenging. Pharmacologic therapy to suppress the rhythm is problematic as many of the antiarrhythmic drugs including Amiodarone may be pro-arrhythmic and have been associated with increased mortality[7, 37-39]. Only Dronedarone, in the ATHENA study, has shown a signal that maintenance of sinus rhythm may reduce CV mortality and hospitalization[40]. Several studies[41-44] including AF-CHF[45] have been conducted to determine whether controlling the rhythm or allowing AF to persist but controlling the ventricular rate is better. The fundamental rationale is that if AF is a marker of adverse outcome, then abolishing the AF rhythm would not affect mortality; hence letting AF persist but keeping the ventricular rate controlled with AV nodal blockade would be sufficient. On the other hand, if AF rhythm is a major instigator of cardiac dysfunction affecting systolic and diastolic function, which further promotes the maintenance of AF, then abolishing AF with maintenance of sinus rhythm would prevent the downward spiralling of heart function and improve mortality.

Figure 1 Percentage of Patients in Sinus Rhythm in Rate versus Rhythm Trials



Thus far, using a drug-based AF rhythm control strategy has not shown any survival benefit compared with a rate control strategy. Of note is that many patients in these antiarrhythmic drug-based rhythm control trials did not maintain sinus rhythm despite assignment to AF rhythm control as shown in **Figure 1**. Indeed the "real" rate of maintenance in sinus rhythm may be much lower as the assessment of heart rhythm in these studies was infrequent; often a single ECG at the time of follow-up visits was used. It is clear that in patients with AF, the frequency of rhythm monitoring determines the likelihood to detect arrhythmias[46]. In addition, a substantial percentage of patients in rate control strategies were found to be in sinus rhythm thereby reducing the likelihood to detect a difference between treatment strategies. In spite of these shortcomings, an analysis of the AFFIRM data suggests that patients maintained in sinus rhythm may have better survival, but the benefit is offset by the adverse effects of antiarrhythmic drugs on survival[47]. An analysis of the data from the DIAMOND study also demonstrated that AF patients with restoration and maintenance of sinus rhythm have better survival than those who remained in AF.[48] This concept is further supported by a recent small trial (CAFÉ II) with higher differential AF suppression between rhythm control and rate control, patients assigned to rhythm control had improved LV function and NT-proBNP.[30] ***Is it possible that better AF rhythm control with higher % maintenance in sinus rhythm, while minimizing harm, can improve survival?***

Catheter ablation to treat AF: Catheter ablation to treat AF has become an effective therapy. The technique of catheter ablation has evolved to include pulmonary vein isolation (PVI) as the "cornerstone" of AF ablation.[49] For patients with paroxysmal AF, PVI can achieve maintenance of sinus in >85% of patients. Success in maintaining sinus rhythm for patients with persistent AF is also improving. PVI along with ablation in the left atrium (LA) is estimated to maintain sinus in ~75% of patients and with antiarrhythmic drug therapy the ability to maintain sinus rhythm is ~85%. A recent multicentre study reported a freedom of AF recurrence rate of 92% in patients with paroxysmal AF and 84% in patients with persistent AF after one or more ablation procedures.[50] A world-wide survey of catheter ablation for AF disclosed a maintaining sinus rhythm rate of 83.2% with paroxysmal AF and 75% with persistent AF.[51] Several randomized controlled trials have demonstrated that catheter ablation for drug refractory AF is superior to further antiarrhythmic drug[52-56] and that this approach may be cost effective.[57, 58] Complications associated with catheter ablation procedure are not insignificant.[59] However the complication rate is comparable to and possibly less than the adverse event rate of antiarrhythmic drugs, although the complications associated with catheter ablation may be more severe. [60, 61] There is also good evidence that after successful catheter ablation for AF, there is reverse remodelling of the LA with decreased LA size and volume without affecting LA function.[62] All these suggest catheter ablation for AF in HF patients is possible and may disrupt the vicious circle of AF and HF.

Catheter ablation of AF in HF patients: Catheter ablation of AF has achieved similar success in HF patients as in patients without HF.[63] Hsu et al reported 78% successful maintenance of sinus rhythm with catheter ablation of AF in HF patients with impaired (LVEF≤45%) LV. Moreover, they observed reverse LV remodelling with marked improvement in LV ejection fraction and reduction of LV dimension.[64] Subsequently, others have reported similar results.[65-67] The improvement of LV function, following catheter ablation for AF, may be due to restoration of atrial transport, better ventricular filling, and enhanced contractility through Starling mechanism; sinus rhythm may also facilitate better rate control. A randomized trial reported that catheter ablation for AF in HF patients with impaired (LVEF≤45%) LV produced better LV ejection fraction, quality of life and 6-minute walk distance than patients treated for rate control with AV nodal ablation and bi-ventricular pacing.[68] Wilton performed a systematic review of catheter ablation of AF in HF patients and compared with patients without HF. He concluded that the success rate and the complication rate are comparable and that there is a 10% improvement of LVEF in HF patients. ***It seems logical to postulate that catheter ablation-based AF rhythm control may provide HF patients with AF better clinical outcome.***

1.2.OVERVIEW OF PREVIOUS STUDIES

1.2.1. Prognostic significance of AF in HF patients

Several studies addressed the prognostic influence of the presence AF in HF. Mamas et al performed a systematic review including 53,969 patients.[36] It revealed that AF is associated with an increased total mortality with an odds ratio (OR) of 1.40 [95% confidence interval (CI) 1.32–1.48, P< 0.0001]. This increase in mortality associated with AF was observed in HF patients with preserved (LVEF>45%) LV as well as in HF patients with impaired (LVEF≤45%) LV. Therefore it is plausible that an effective therapy to restore and maintain sinus rhythm may be beneficial in HF patients with preserved (LVEF>45%) or impaired (LVEF≤45%) LV. ***The current study is designed to address this with an effective AF rhythm control strategy.***

1.2.2. Catheter ablation techniques and outcome

Parkash et al performed a systematic review of the various ablation techniques for AF ablation. For paroxysmal AF, pulmonary vein (PV) antral ablation with PV isolation is preferred with higher success rate. For non-paroxysmal AF, apart from PV isolation, additional LA ablation is necessary to ensure less AF recurrence and more than one ablation session is often needed. Brooks et al did a systematic review of outcomes of patients with long-standing persistent AF. They concluded that the optimal ablation technique is unclear, as long as the ablation includes PV antral ablation with isolation and LA ablation (targeting complex fractionated electrogram or LA lines or box lesion) long-standing persistent AF can be effectively treated (~85% AF suppression) with a composite of extensive LA catheter ablation with repeat procedure and/or pharmacueticals.[69] ***This is the approach to be used in the catheter ablation-based AF rhythm control strategy of this trial. (See section 6.3.2)***

1.2.3. Ablation-based AF rhythm control is superior to drug-based rhythm control

There have been several randomized controlled trials comparing the efficacy (lack of AF recurrence) of catheter ablation-based AF rhythm control vs. antiarrhythmic drug-based rhythm control. Most of the studies included patients with drug-refractory symptomatic AF and one study included patients not previously on antiarrhythmic drug. All the studies demonstrated a marked reduction of AF recurrence with catheter ablation. Systematic reviews of these studies concluded that catheter ablation for drug-refractory symptomatic AF is effective for rhythm control and that a longer study with mortality endpoint is needed.[60, 70-72] ***Therefore, this is an objective of this trial.***

1.2.4. Catheter ablation-based AF rhythm control in HF patients

Wilton et al performed a systematic review of the literature of 7 observational studies and one randomized controlled trial that compared the effectiveness and safety of catheter ablation-based AF rhythm control in HF patients and patients without HF. The AF recurrence rate is higher in HF patients after one procedure, but with one or more procedures the AF recurrence rate is no longer different suggesting that more than one ablation procedure is often needed in HF patients. They also found a significant improvement of LV function averaging 11%. The complication rate of the ablation procedures is comparable between those with or without HF.[29] ***These data are encouraging indicating catheter ablation-based rhythm control is a reasonable option for HF patients with AF and that a trial to compare catheter ablation-based rhythm control with rate control is timely.***

1.2.5. Previous studies with similar study design

This team of investigators has conducted several large-scale studies successfully. The recently completed RAFT study is a 1798 patient trial of arrhythmia device management in HF patients. Data coordination team and participating centres are largely the same. There has been excellent communication between the study centres and the coordinating centre from the RAFT study, which will facilitate the conduction of the RAFT-AF trial. Dr. Verma conducted the STAR-AF trial, [73] which was a study to investigate the optimal ablation techniques for the treatment of AF. The STAR-AF study was completed with largely the same groups of investigators. Dr. Talajic is a co-leader of the CIHR funded AF-CHF trial, which compared antiarrhythmic drug-based rhythm control with rate control in HF patients. This team of investigator has the experience and track record to conduct a trial of this nature. The conduct of these studies can be seen as pilot to

indicate the ability to recruit patients for the RAFT-AF trial, the ability to coordinate the size and complexity of RAFT-AF, and the ability to complete a trial like RAFT-AF.

1.3.OTHER ON-GOING AF CATHETER ABLATION TRIALS

A few clinical trials focusing on AF ablation are being conducted. They are significantly different from RAFT-AF. The CABANA study plans to include 3000 patients with AF and one risk factor of thromboembolism comparing catheter ablation of AF vs. either antiarrhythmic drug rhythm control or rate control with a primary endpoint of all-cause mortality. This study will not have many HF patients. Two trials (Catheter Ablation versus STandard conventional treatment in patients with LV dysfunction and Atrial Fibrillation (CASTLE-AF) and (AMICA) Atrial fibrillation Management In Congestive heart failure with Ablation) focus on HF patients with impaired LV and AF. In both studies, catheter ablation is compared to antiarrhythmic drug rhythm control in HF patients with impaired LV (EF<35%) implanted with an ICD/CRT and has paroxysmal and persistent AF. Both studies are conducted by the device industry. The primary endpoint of the former study is a composite of all-cause mortality or HF hospitalization, and that of the latter study is on LVEF. Neither study will determine if the "best" AF rhythm control is better than the "best" rate control in HF with either impaired or preserved LV. Neither study will likely have enough power to determine the effect of catheter ablation-based rhythm control on cardiovascular mortality.

1.4.SCIENTIFIC RATIONALE FOR CURRENT STUDY

The need for a study to guide better management of AF in HF patients is evident for the following reasons:

- **AF is recognized to be a major health issue.** The need for *clinical trial evidence to guide better management of AF is a top priority as illustrated by a recent announcement: "Compare the effectiveness of treatment strategies for atrial fibrillation including surgery, catheter ablation, and pharmacological treatment*" has been identified by the Institute of Medicine of the US National Academes to be the top priority topic for comparative effectiveness research.[74] Being two increasingly prevalent and frequently coexisting cardiac conditions, recent editorials and reviews identified that "*there is a need for large randomized trials that are powered to assess potential survival benefits of AF patients with HF*".[75-78]
- **There is good evidence that HF patients with AF have increased mortality and morbidity.** The management of AF in HF patients with impaired LV function has been studied in AF-CHF and CAFÉ II trials to identify if antiarrhythmic drug-based AF rhythm control is beneficial versus heart rate control. While the bigger AF-CHF trial did not show any survival benefit, the smaller CAFÉ II trial (not powered for survival) showed an improvement in LV function and NT-proBNP as surrogate markers of survival. A major criticism of the rate versus rhythm control trials is that antiarrhythmic drug-based AF rhythm control is not very effective in suppressing AF. The differences of AF detected in follow-up between antiarrhythmic drug-based AF rhythm control and heart rate control is only 28% in AFFIRM, 47% in AF-CHF **(Figure 1)**. The management of AF in HF patients with preserved (LVEF>45%) LV is clinically challenging and there is no data to guide AF therapy as evident by the absence of commentary in the 2009 ACCF/AHA focused updated HF guidelines[79], a level C evidence to recommend heart rate control and also a level C evidence to recommend restoration and maintenance of sinus rhythm in the 2005 ACC/AHA HF guidelines.[80]

- **Progress in the understanding, technique and technology of catheter ablation.** Since the initial attempts of catheter ablation to rhythm control in 1998,[81] there has been substantial progress in the understanding, technique and technology of catheter ablation such that the procedure is becoming mainstream treatment in patients with clinically problematic AF. Clinical trials have demonstrated that catheter ablation AF rhythm control is superior to antiarrhythmic drug AF rhythm control in patients with drug refractory symptomatic AF. In clinical trials and in a worldwide survey[61] catheter ablation for AF rhythm control has been found to be a relatively safe, effective and cost-effective therapy.[58] The 2010 European Society of Cardiology guidelines for the management of AF indicated, "*There is a clear need for a controlled trial to assess the effects of catheter ablation and safe antiarrhythmic drugs as novel means for sinus rhythm maintenance on severe cardiovascular outcomes compared with rate control*".[82]
- **Feasibility and success of catheter ablation in HF.** Since Hsu's report of catheter ablation-based AF rhythm control in HF patients with impaired LV function, several reports substantiated their results attesting to the feasibility of performing catheter ablation in HF patients, and that the success rate is as good as in patients without HF. Moreover there is evidence of significant improvement of LV function and in a randomized controlled trial, catheter ablation-based AF rhythm control was superior to rate control with AV nodal ablation and biventricular pacing with better QOL, exercise capacity and higher LV ejection fraction.[68]

1.5.SUMMARY OF BACKGROUND AND RATIONALE

AF in HF patients is common and the management is a difficult clinical problem. Recognizing 1) the high likelihood of HF progression with poor prognosis even with good rate control, 2) antiarrhythmic drug therapy to manage sinus rhythm is not beneficial and 3) catheter ablation is effective to abolish AF but has not been shown to be effective in improving mortality and morbidity, physicians are faced with the dilemma of allowing AF to persist and institute rate control or aggressively abolishing AF and maintaining sinus rhythm using catheter ablation technique with or without antiarrhythmic drugs. ***Therefore the time is right to conduct a catheter ablation-based AF rhythm control versus rate control trial in patients with HF and high burden AF.***

1.6.POTENTIAL RISKS AND BENEFITS

1.6.1. Risks

Wilton's systematic review identified that the risk of catheter ablation-based AF rhythm control have similar procedure risk in patients with or without HF.[83] However, there are distinct risks of ablation procedure, which will be explained to the patient upon consenting to the trial. This includes 0.15% death, 1.3% tamponade, 0.2% stroke, 0.3% PV stenosis, and 0.04% atrial-esophageal fistula.[61] The risks of rate control are bradycardia needing a pacemaker, and intolerance of rate control drugs. The risk associated with catheter ablation of the patients will be monitored closed and compiled by an expert panel headed by Drs. Macle and Skanes (see section 13) and reported to the Data Monitoring Committee for review.

1.6.2. Benefits

The result of this study will have a direct impact on the management of AF in HF patients. If rate control were superior to catheter ablation-based rhythm control then the treatment would be

optimal HF therapy and rate control. On the other hand if catheter ablation-based rhythm control were superior then this option would be considered as the treatment of choice in this population. This will have a profound impact to the management of these patients and will likely change practice guidelines.

2. STUDY HYPOTHESIS

Catheter ablation-based AF rhythm control, as compared with rate control, will reduce all-cause mortality and heart failure events (*defined as an admission to a healthcare facility for > 24 hours or clinically significant worsening heart failure leading to an intervention (defined as treatment in an emergency department, a same-day access clinic, or an infusion centre) or unscheduled visits to a healthcare provider for administration of an intravenous diuretic as accepted by FDA and an increase in chronic heart failure therapy; see definition in Appendix O, June 2019)* in patients with AF and HF of either impaired left ventricular function (LVEF ≤ 45%) or preserved LV function (LVEF >45%).

3. STUDY OBJECTIVES

3.1.OBJECTIVES

3.1.1. Primary Objective

In patients with HF, either impaired (LVEF≤45%) or preserved (LVEF>45%) LV function and high burden AF, to determine if catheter ablation-based rhythm control of AF, as compared with rate control , will reduce all-cause mortality and heart failure events (*defined as an admission to a healthcare facility for > 24 hours or clinically significant worsening heart failure leading to an intervention (defined as treatment in an emergency department, a same-day access clinic, or an infusion centre) or unscheduled visits to a healthcare provider for administration of an intravenous diuretic as accepted by FDA and an increase in chronic heart failure therapy) (see definition in Appendix O, June 2019)*

3.1.2. Secondary Objective

To determine, in patients with HF (either impaired (LVEF≤45%) or preserved (LVEF>45%) LV function and high burden AF:

A. Reduce all-cause mortality
B. Reduce heart failure events*
C. Improve QOL (as determined by MLWF, EQ5D and AFEQT questionnaires)
D. Improve exercise capacity (as determined by 6 Minute Hall walk distance)
E. Reduce NT-proBNP at 1 year and at 2 year follow-up**
F. In patients with HF, impaired (LVEF≤45%) LV function and high burden AF, to determine if catheter ablation-based rhythm control of AF, as compared with rate control, will reduce all-cause mortality and heart failure events*
G. In patients with HF, preserved (LVEF>45%) LV function and high burden AF, to determine if catheter ablation-based rhythm control of AF as compared with rate control will reduce all-cause mortality and heart failure events *
H. Be more cost effective

** Heart failure events (defined as an admission to a healthcare facility for > 24 hours or clinically significant worsening heart failure leading to an intervention (defined as treatment in an emergency department, a same-day access clinic, or an infusion centre) or unscheduled visits to a healthcare provider for administration of an intravenous diuretic as accepted by FDA and an increase in chronic heart failure therapy (see definition in Appendix O, June 2019)*

*** In a subset of sites in Canada: NT-proBNP (BNP) values, Echocardiogram measures of LV function, AF Burden (14 day Continuous ECG Monitoring)*

3.2. OUTCOME MEASURES

3.2.1. Primary Outcome Measures

Composite of all-cause mortality and hospitalization for heart events (*defined as an admission to a healthcare facility for > 24 hours or clinically significant worsening heart failure leading to an intervention (defined as treatment in an emergency department, a same-day access clinic, or an infusion centre) or unscheduled visits to a healthcare provider for administration of an intravenous diuretic as accepted by FDA and an increase in chronic heart failure therapy (see definition in Appendix O, June 2019)*. All the deaths and HF events will be recorded and reported to the coordinating centre with a detailed description of the circumstances surrounding the event on a case report form along with copies of source documentation. An event adjudication committee co-chaired by Dr. J Healey and G. Newton will determine the cause of death and the cause of admission to hospital based on predetermined criteria. The committee will be blinded to the treatment allocation of the patients.

3.2.2. Secondary Outcome Measures

1) Reduce all-cause mortality; 2) Reduce HF events; 3) Improve QOL (as determined by MLWF, EQ5D and AFEQT questionnaires4) Improve exercise capacity (6 minute hall walk) 5) Reduce NT-proBNP at 1 & 2 Year Follow up**; 6 &7) In patients with HF, impaired (LVEF≤45%) or preserved (LVEF>45%) LV function and high burden AF, to determine if catheter ablation-based rhythm control of AF, as compared with rate control, will reduce all-cause mortality and heart failure events.); 8) Be more cost-effective

3.2.3 Safety Outcome Measures

Thromboembolic events, Symptomatic PV stenosis, Atrio-esophageal fistula, Pericardial effusion requiring pericardiocentesis, major bleeding requiring blood transfusion, amiodarone induced thyroid, pulmonary and other toxicity.

4. STUDY DESIGN

4.1.TRIAL DESIGN

This is a Phase 4, multi-centre prospective randomized open study with blinded endpoint assessment (i.e. PROBE design)[84]

4.2.ENROLLMENT TARGET
A total of 600 patients will participate in this study in a minimum of 30 centres. Patients will be randomized in a 1:1 ratio to each treatment arm.

4.3.RANDOMIZATION
1:1 allocation randomization ratio to ablation-based AF rhythm control versus rate control, with randomization stratified by centre, by impaired (LVEF ≤ 45%) versus preserved (LVEF > 45%) LV function and by AF category.

4.4.TRIAL INTERVENTIONS
This trial will compare two management strategies for patients with high burden AF and HF with impaired (LVEF≤45%) or preserved (LVEF>45%) LV function. The two arms of the study are 1) rate control and 2) catheter ablation-based AF rhythm control. See Section 6 and Appendices B and C for details.

4.5.EXPECTED DURATION
Based on our experience of the rate and pattern of accrual in the RAFT trial, an accrual over 3 years with a minimal follow-up of 2 years was selected. A minimum follow-up of two years will give a median follow-up of ~54 months. This is an adequate amount of time to observe if the intervention has lasting effect and will allow the intervention to derive any significant benefit on this patient population.

Many of the AF catheter ablation studies reported outcome up to 1 year. There is a need for longer-term outcome data to ensure the short-term result of AF suppression is upheld to a longer-term period. If catheter ablation-based AF rhythm control in HF patients is to be implemented into clinical practice it is necessary to demonstrate that this invasive therapy affects longer-term outcome.

4.6.PROTECTING AGAINST SOURCES OF BIAS
This is a multi-centre prospective randomized open blinded endpoint trial (PROBE) design.[84] The nature of this study does not allow us to use a double-blinded approach with sham procedure. This is specifically addressed in the expert consensus statement on AF ablation.[49] The PROBE design has been used extensively in hypertensive clinical trials and more recently has been adopted in clinical trial of cardiac therapy[85] and AF treatment.[86] It has been suggested for PROBE design trials, hard endpoints should be used as the primary outcome.[87]
In this trial, the primary endpoint is a composite of all-cause mortality and HF Event (*defined as an admission to a healthcare facility for > 24 hours or clinically significant worsening heart failure leading to an intervention (defined as treatment in an emergency department, a same-day access clinic, or an infusion centre) or unscheduled visits to a healthcare provider for administration of an intravenous diuretic as accepted by FDA and an increase in chronic heart failure therapy (see definition in Appendix O, June 2019)*

We have taken the following steps to minimize biases:

- *Selection bias* is addressed by allocation concealment using central randomization and safe guards to ensure the assigned treatment is allocated to that specific patient.
- *Performance and attrition bias* (care provided in the two treatment groups are the same) is minimized by ensuring all patients receiving appropriate HF and cardiac treatment

before entry into the study and that the patients receiving standardized HF management in subsequent follow-up.

- *Detection bias* (detection of outcome in the two treatment groups are the same) is minimized, as the primary endpoint of this study is a "hard endpoint" – all-cause mortality and HF event; a blinded adjudication committee will adjudicate the causes of death and hospital admission. Standardized questions regarding event and standardized quality of life questionnaires will be used to minimize the bias and collection of these secondary outcome measures.

5. ELIGIBILITY CRITERIA

5.1. INCLUSION CRITERIA

Patients meeting all of the following criteria are eligible for inclusion in the study.

1. Patients with one of the following AF categories and at least one ECG documentation of AF:
   a) High burden Paroxysmal defined as ≥ 4 episodes of AF in the last 6 months, and at least one episode > 6 hours (and no other episodes that required CV or was > 7 days)
   b) Persistent AF (1) defined as ≥ 4 episodes of AF in the last 6 months, and at least one episode > 6 hours, and at least one AF episode less than 7 days but requires cardioversion. No AF episodes are > 7 days
   c) Persistent AF (2) as defined by at least one episode of AF > 7 days but not > 1 year
   d) Long term persistent AF defined as an AF episode, at least one year in length and no episode > 3 years
2. Optimal therapy for heart failure of at least 6 weeks (according to 2009 ACCF/AHA class 1 recommendations).
3. HF with NYHA class II or III symptoms with either impaired LV function (LVEF ≤ 45%) as determined by EF assessment within the previous 12 months or preserved LV function (LVEF > 45%) as determined by EF assessment within the previous 12 months
4. An elevated N-terminal pro brain natriuretic peptide (NT-proBNP) defined as:
   A) Patient has been hospitalized for Heart Failure* in the past 9 months, ha**s** been discharged AND:
   i- Is presently in Normal Sinus Rhythm and NT-pro BNP is ≥ 400 pg/mL or
   ii- Is presently in Atrial Fibrillation and NT-pro BNP is ≥ 600 pg/mL
   OR
   B) Patient has had no hospitalization for Heart Failure in the past 9 months AND:
   i- Has had paroxysmal Atrial Fibrillation, is presently in Normal Sinus Rhythm and NT-proBNP is ≥ 600 pg/mL or
   ii- Is presently in Atrial Fibrillation and NT-proBNP is ≥ 900 pg/mL

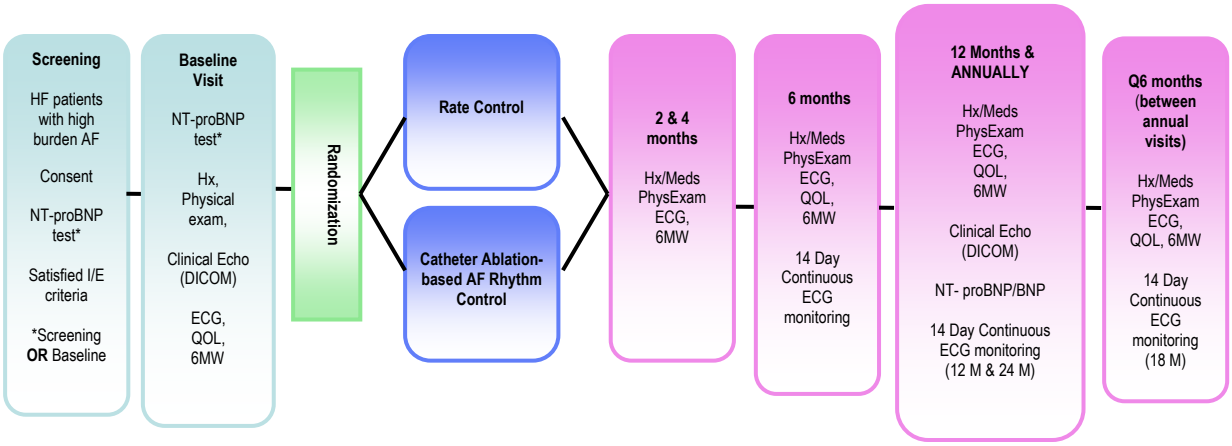
   *Heart Failure Admission is defined as admission to hospital > 24 hours and received treatment for Heart failure
5. Suitable candidate for catheter ablation or rate control therapy for the treatment of AF
6. Age ≥18

5.2. EXCLUSION CRITERIA

Patients will be excluded from the trial if they:

1. Have an LA dimension > 55 mm as determined by an echocardiography within the previous year
2. Had an acute coronary syndrome or coronary artery bypass surgery within 12 weeks
3. Have rheumatic heart disease, severe aortic or mitral valvular heart disease using the AHA/ACC guidelines
4. Have congenital heart disease including previous ASD repair, persistent left superior vena cava
5. Had prior surgical or percutaneous AF ablation procedure or atrioventricular nodal (AVN) ablation
6. Have a medical condition likely to limit survival to < 1 year
7. Have New York Heart Association (NYHA) class IV heart failure symptoms
8. Have contraindication to systematic anticoagulation
9. Have renal failure requiring dialysis
10. AF due to reversible cause e.g. hyperthyroid state
11. Are pregnant
12. Are included in other clinical trials that will affect the objectives of this study
13. Have a history of non-compliance to medical therapy
14. Are unable or unwilling to provide informed consent

6. STUDY METHODOLOGY



A detailed study schedule of events can be found in Appendix A.

6.1.PRE RANDOMIZATION

6.1.1. Screening/Consent

- All patients must receive optimal medical therapy for heart failure as per ACC/AHA/HRS guideline for drug and ICD/CRT

- Optimal medical therapy
    - for impaired (LVEF≤45%) LV function include > 6 weeks treatment with: therapeutic dose of beta-blocker, ACEI or ARB, spironolactone, diuretic
    - ICD and CRT in appropriate patients according to AHA/ACC guideline
    - For preserved (LVEF>45%) LV function include: diuretic, beta-blocker
- Treatment period
    - **6 months** to administer all appropriate treatment in both arms
    - Catheter ablation-based rhythm control strategy – first ablation within 2 weeks
    - Rate control strategy

Details on the consent procedure are provided in Section 12.2. The study will be explained to the patient by study physician/research staff. Following consent, a preliminary blood test (NT-proBNP) will be performed by the study team to determine whether or not this study is suitable for you. Following the signing of the informed consent form (ICF), and if applicable, an eligible patient will be asked to stop all amiodarone and antiarrhythmic medications until after randomization and treatment arm has been established.
For sites without access to NT-proBNP clinical values, the consent may be a two stage process. The first consent will request a study NT-proBNP measure and if the patient meets inclusion criteria based on the NT-proBNP results, a second consent will be introduced consenting to the RAFT-AF study.

6.1.2. Baseline Visit

After a qualified patient has consented for the study, a baseline clinical exam will be scheduled. The baseline visit will include: patient and cardiovascular history, 12-lead ECG, review of recent echocardiography (within the previous 12 months), quality of life assessment, medication assessment, 6-minute walk test, review of the patient's most recent blood chemistry profile including liver, renal, thyroid (within the previous 6 months). Retrospective Baseline echocardiogram will be performed in a standardized manner (DICOM format). In addition to the clinical echocardiograms being analysed at the site, we will request the baseline clinical echocardiogram be de-identifed and be sent to an echocardiogram core centre (London Health Sciences Centre) to review and measure parameters. The personnel at the echocardiogram core centre will be blinded to the patient's treatment allocation.
Randomization will then occur following the completion of the baseline visit.

6.2. RANDOMIZATION

1:1 allocation randomization ratio to ablation-based AF rhythm control versus rate control, with randomization stratified by centre, by impaired (LVEF ≤ 45%) versus preserved (LVEF > 45%) LV function. Central randomization with web-based technology will be used. The centre coordinator will access the automated web based system and will provide pertinent information such as date of birth of the eligible patient to be randomized. The treatment allocation will then be assigned by this automated system.

6.3.TREATMENT ARMS

6.3.1. Rate Control Group

- HR<80 at rest
- HR<110 at 6 MW distance
- Use beta-blockers, calcium channel blockers (if not contra-indicated), digitalis and in combination
  - Cannot use dronedarone, or amiodarone for rate control
- AVN ablation with bi-ventricular pacing if heart rate is not controlled with medication
- No cardioversion is permitted
- No anti-arrhythmic drug is permitted except for adjunct to ICD treatment for ventricular arrhythmia

Patients randomized to rate control therapy will be assessed immediately following randomization. They will have rate control assessment to ensure heart rate is adequately controlled using the criteria used in the AF-CHF and AFFIRM trials: resting heart rate HR < 80 bpm and heart rate <110 bpm at 6 minute walk distance. A lenient heart rate regimen[88] is not used in this trial, as it has not been adequately verified in HF patients. Beta-blocker, Calcium channel blocker (in patients with preserved LV function) and Digoxin can be used in combination. If heart rate is still not controlled with medication then AV nodal ablation and implantation of biventricular pacemaker may be used. In the AF-CHF trial 97% of patients were successfully rate controlled using drug therapy alone. Restoration of sinus rhythm should NOT be attempted with cardioversion or with antiarrhythmic drug. Antiarrhythmic drugs cannot be used for rate control. Antiarrhythmic drugs can only be used for the control of ventricular arrhythmia, usually as adjunctive therapy to ICD therapy in appropriate patients according to the ACC/AHA guidelines. (See Appendix B for rate control strategy algorithm)

6.3.2. Catheter ablation-based rhythm control group

Patients randomized to catheter ablation-based rhythm therapy are to have the following:

A) Pre-ablation preparation:

- Pre-ablation preparation
  - Anticoagulation
    - Any approved oral anticoagulation drug for a minimum of 4 weeks
    - In patients on Warfarin, the following options may be applied:

1. Warfarin may be continued, provided the INR is ≤ 3.0.
2. Optional with Warfarin is bridge in and bridge out 4 days LMWH, ½ dose out for 5 days

    - Any approved oral anticoagulation drug to be continued indefinitely regardless of ablation success
    - IV Heparin intra-procedure - 100 units/kg bolus + infusion 15units/kg/hr
    - ACT > 250 sec

- All anti-arrhythmia drugs (other than amiodarone) are to be stopped before ablation procedure for 5 half life, amiodarone is to be stopped for 6 weeks

The patients must be fully anticoagulated for at least 4 weeks, and warfarin may be continued, provided the INR is ≤ 3.0. Optional with Warfarin is bridge in and bridge out 4 days LMWH, ½ dose out for 5 days prior to the ablation procedure. All oral anticoagulants that are market released are approved for use during the study. All antiarrhythmic drugs must be terminated for 5 half-life and Amiodarone for 6 weeks prior to the ablation procedure. Pre-procedure imaging (contrast enhanced computed tomography, CT, cardiac magnetic resonance, MR) to identify the anatomy and perform 3-D reconstruction of LA and PVs is to be done at the discretion of the investigator and centre. Pre-procedure transesophageal echo to detect LA thrombus is to be done at the discretion of the investigator and centre.

B) Catheter ablation technique:

Equipment to be used for catheter ablation:

- 3D mapping system (NavX or Carto)
- Irrigated catheter

Catheter Ablation technique

- Conscious sedation or GA at the discretion of the investigator, data will be collected
- RF setting – 43 degree C, <30 watts posterior LA, <40 watts anterior LA
- Esophageal temperature monitoring optional
- PVI all PV wide antral ablation with demonstration of entrance and exit block
- For patients with paroxysmal AF only, PVI plus at least one of the following: roof line, mitral line, CFE
- For all other patients, PVI and at least one the following:
    - Roof and mitral (anterior or posterior) lines
    - Roof line + CFE
    - Mitral line + CFE
    - CFE as defined use mapping system
    - Observed RA or LA flutter – need to be ablated
    - Cardioversion at the end of the procedure if the patient is still in AF after the ablation procedure

Discharge instructions:

- Discharge medications: anticoagulation, Antiarrhythmic is encouraged to be used for only 6 weeks post-ablation (amiodarone or dofetilide for impaired (LVEF≤45%) LV and amiodarone or dofetilide for preserved (LVEF≤45%) LV
- Proton pump inhibitor, sulcrate are to be used at the investigator's discretion
- If AF/AT/Aflutter recurred after first procedure, a second ablation procedure is strongly recommended
- May use amiodarone or dofetilide in the impaired (LVEF≤45%) LV function study if the patients have recurrent AF/flutter after two or more ablation procedures
- May use amiodarone or dofetilide in the preserved (LVEF≤45%) LV function study if the patients have recurrent AF/flutter after two or more ablation procedures

The ablation procedure can be performed under conscious or general anesthesia. The use of esophageal temperature monitoring and intra-cardiac echocardiographic imaging during the ablation procedure is optimal. After trans-septal punctures, the patients must receive IV heparin to keep the activated clotting time (ACT) greater than 250 seconds throughout the rest of the procedure. A saline open-irrigated radiofrequency ablation catheter must be used for ablation. The radiofrequency ablation settings are to be the following: catheter temperature no more than 43ºC, power setting of no more than 30 Watts for ablation of the posterior LA and no more than 40 Watts for ablation of the rest of LA. Catheter ablation must consist of PV antral ablation with confirmation of PV entrance and exit conduction block[89] and one of the following LA substrate modifying ablation : 1) LA roof and mitral isthmus lines with confirmation of bidirectional block, 2) ablation targeting complex fractionated electrograms based on mapping with an automated algorithm (either the Carto ot NavX system). If a combined linear and electrogram strategy is to be employed as an adjuvant to PV antral ablation, the following need to be performed 3) LA roof line with confirmation of bidirectional block and ablation targeting complex fractionated electrograms based on mapping with an automated algorithm (either the Carto or NavX system), or 4) LA mitral line with confirmation of bidirectional block and ablation targeting complex fractionated electrograms based on mapping with an automated algorithm (either the Carto or NavX system). The reason to allow the options stated above is because the main objective is to perform LA substrate modifying ablation, but the exact method to do so is less important for the outcome of AF rhythm control.

For CFE ablation using the automated algorithm, the endpoint should be total elimination of all electrograms within the clusters/regions of CFE. Ablating to the point of CFE regularization and leaving behind residual signals is not sufficient and may lead to future micro or macro re-entry. All CFE regions in the LA should be targeted even if AF terminates to sinus or an organized atrial arrhythmia. If AF does not terminate, then CFE ablation should be performed in the CS and RA.

To assess block across the roof and mitral lines, the following methods are suggested. To assess the block across the roof line can be confirmed by demonstrating that the activation sequence of the posterior LA is caudocranial instead of craniocaudal. This can be shown by pacing from the left atrial appendage. If the ablation catheter is placed on the low posterior LA, the pace to local EGM delay will be less than when the ablation catheter is placed in the high posterior LA, closer to the roof line. In the case where the roof line is assessed after creation of a line of block at the mitral annulus, activation of the posterior LA occurs not only low to high, but also right to left (pacing in LAA). Again, you can show this by demonstrating a shorter pace to EGM delay on the right posterior LA compared to the left posterior LA. To assess the block across a posterior mitral line, pacing lateral to the line in the LA appendage from the ablation catheter should result in a proximal-distal activation sequence along the CS. With the ablation catheter still lateral, pacing from the proximal CS should result in a delayed activation in the ablation catheter (usually more than 90-100 msec). To assess the block across an anterior mitral line, place the pacing catheter just medial to the line and the circular mapping catheter in the LA appendage. Pace from the ablation catheter along the entire medial aspect of the line and the delay from the ablation catheter to the LA appendage should be at least 90-100 msec along the entire line. Alternatively, pacing along the line should demonstrate double potentials along the entire line. Finally, complete linear block can also be confirmed if pacing laterally to the line results in a distal to proximal CS activation pattern, while after dragging the catheter to the septal side of the line, the CS is activated from proximal to distal.

If RA or LA flutter/tachycardia is encountered (either induced or spontaneous), the strategy chosen above should be completed and if required, mapping and ablation to terminate the flutter/tachycardia must be performed. If the patient remains in AF upon completion of the chosen ablation strategy, cardioversion to restore sinus rhythm is to be performed. After the patient has returned to sinus rhythm, entrance and exit block of all PV and bidirectional conduction block of any LA lines are to be checked and confirmed.

C) Post-ablation treatment: Patients are generally kept in the hospital up to 24 hours for observation after the ablation procedure. The patient must continue on anticoagulation therapy. Antiarrhythmic drugs may be used for 4-6 weeks after the ablation to reduce post-ablation atrial arrhythmia.[90] Proton pump inhibitor can be used for 4 weeks after the ablation to reduce the risk of atrio-esophageal fistula.[91]

D) AF recurrence after ablation: In this patient population of high burden AF and HF, it is expected that one ablation procedure may not be sufficient to accomplish complete AF rhythm control. For patients with AF or atrial flutter/tachycardia recurrence, a second or third ablation is highly recommended and encouraged. AF or atrial flutter/tachycardia recurrence is defined as <75% reduction of AF/atrial flutter/tachycardia burden. There should be at least a 6-week period between ablation procedures to reduce complications and to allow healing. A repeat ablation procedure should be performed in the same manner as the first ablation procedure described above. At least two procedures are strongly recommended and this should be discussed with the patient at the onset of patient recruitment. (See Appendix C for catheter ablation-based AF rhythm control strategy algorithm)

E) Antiarrhythmic drug use: Antiarrhythmic drugs can be used for 4-6 weeks to reduce immediate post-ablation arrhythmia. Antiarrhythmic drugs are not encouraged as a means for long-term AF rhythm control. However, antiarrhythmic drug can be used if needed as adjunctive therapy for AF suppression after at least two ablation procedures. In this situation the antiarrhythmic drug to be used are Amiodarone or Dofetilide in patients with impaired (LVEF≤45%) LV function and Amiodarone or Dofetilide in patients with preserved (LVEF>45%) LV function.

6.4.FOLLOW UP VISITS

The patients will be followed at 2, 4 and 6 months and then every 6 months. A physical assessment and 6-minute walk distance will be performed at all follow-up visits. Quality of life assessment will also be done at specified visits. In addition, at specified visits, Echocardiogram, NT-proBNP (BNP) measures and 14 day Continuous ECG Monitoring will be collected.
See Schedule of Events (Appendix A) for details.

7. STUDY PROCEDURES

Detailed operating manuals will be provided to each study centre by the coordinating centre.

7.1.CLINICAL EVALUATIONS

Data will be collected at baseline and at follow-up visits. At each visit, a medical history will be performed to ascertain if there have been changes of HF status, change in medications, and if there have been any HF events (*defined as an admission to a healthcare facility for > 24 hours or clinically significant worsening heart failure leading to an intervention (defined as treatment*

in an emergency department, a same-day access clinic, or an infusion centre) or unscheduled visits to a healthcare provider for administration of an intravenous diuretic as accepted by FDA and an increase in chronic heart failure therapy (see definition in Appendix O, June 2019). A 12-lead ECG will be performed. The patient's most recent blood chemistry profile including liver, renal, thyroid and NT-proBNP (if available) levels will be reviewed. NT-proBNP (or BNP) will be requested at baseline, 12 month follow-up and annually. In addition, at the 6, 12, 18 and 24 month follow up visits, a 14 Day Continuous ECG Monitoring will be collected. Questionnaires will be completed: The Minnesota living with heart failure questionnaire (MLWHF) is an often used and validated disease specific QOL measure; EQ5D-3L is a well used and validated generic QOL measure (Appendices D, E, F); The Atrial Fibrillation Effect on quality-of –life (AFEQT) is a newly validated instrument to evaluate QOL in patients with AF (Appendix G)[92]. In addition, the Canadian Cardiovascular Society Severity in Atrial Fibrillation (CCS-SAF) scale will be used at each study visit which is an assessment of the patient's quality of life performed by the investigator (Appendix H) [93]. A 6 minute walk test will be performed and the walk distance will be collected (protocol to conduct the test is in Appendix I). In addition, at the 12 month follow up and annually, an echocardiogram and NT-proBNP (or BNP) measure will be collected. The 12 month and annual echocardiograms will be performed in a standardized manner (DICOM format). In addition to the clinical echocardiograms being analysed at the site, we will request these clinical echocardiogram be de-identifed and be sent to an echocardiogram core centre (LHSC) to review and measure parameters. The personnel at the echocardiogram core centre will be blinded to the patient's treatment allocation.

7.2. LABORATORY TESTS

7.2.1. NT-proBNP

A blood test to assess NT-proBNP levels will be performed at the screening visit (following informed consent), at 12 months and annually. Blood samples will be disposed of immediately following the visit.

8. ASSESSMENT OF SAFETY

8.1 DATA MONITORING COMMITTEE (DMC)

A data monitoring committee will be set up. A three person DMC will consist of an electrophysiologist, a HF specialist and a biostatistician with trial expertise. A charter governing the operations of the DMC will be developed in conjunction with DMC to determine specific procedures such as the frequency of reports/meetings and content of the safety analyses reports, including:

- Adverse Events
- Serious Adverse Events
- Type and Duration of Follow-up of Subjects after Adverse Events
- Reporting Procedures
- Reporting of Pregnancy

8.2 SAFETY REPORTING

Definitions

8.2.1 Adverse Event (AE)

An AE or adverse experience is:

Any untoward medical occurrence in a patient or clinical investigation participants, which does not necessarily have to have a causal relationship with this treatment.
An AE can therefore be any unfavourable and unintended sign, symptom or disease temporally associated with the study, whether or not considered related to the study.

8.2.2 Serious Adverse Event (SAE)

A serious adverse event is any untoward medical occurrence that:

- Results in death,
- Is life-threatening,
- Requires inpatient hospitalisation or prolongation of existing hospitalisation,
- Results in persistent or significant disability/incapacity, or
- Is a congenital anomaly/birth defect.
- Other important medical events.

A detailed data monitoring/safety manual will be provided to each study centre by the coordinating centre.
The collection of Serious Adverse Events will not commence **until** the patient is randomized.
Please note, for patients in the rate control arm admitted to hospital for an Atrio-ventricular node ablation, this is not considered a serious adverse event.
Please note, for patients in the rhythm control arm (ablation) admitted to hospital for a redo Atrial Fibrillation ablation, this is not considered a serious adverse event.

8.2.3 Protocol Deviations

Protocol violations and deviations should be reported promptly to the REB if they meet the following criteria:

a) If there is a deviation from the protocol to eliminate an immediate hazard to the patient.
b) If there is a change to the protocol that increases the risk to the patient and/or significantly increases the conduct of the trial.
c) A copy of the deviations submitted to the REB should be filed in the Regulatory Binder.

8.3 DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

Direct access will be granted to authorised representatives from the sponsor, host institution and the regulatory authorities to permit trial-related monitoring, audits and inspections.

9. STATISTICAL CONSIDERATIONS

9.1.STATISTICAL ANALYSIS/SAMPLE SIZE

9.1.1 Event rate: Control Arm (rate control group):

The composite end point rate was estimated to be 17% per year. This was based on review of several clinical trials including DIAMOND,[48] CHARM,[94] and AF-CHF.[45]

9.1.2 Minimal Clinically Important Difference (MCID:

Previous rate versus rhythm control trials were reviewed for the selection of the relative risk reduction (RRR) for the MCID, in particular for studies with a primary endpoint of CV mortality the choice for RRR was 25% for comparing drug treatments in AF-CHF.[96] Given the invasive nature of catheter ablation therapy, a larger RRR must be realized before this therapy should be adopted. A RRR of 30% was selected based on a consensus of the RAFT-AF investigators.

9.1.3 Event rates: Rate control group and catheter-based AF rhythm control group:

Based on the 30% RRR and the 17% annual event rate for the rate control group, the annual composite of all-cause mortality and heart failure event rate for the catheter-based AF rhythm control ICD/CRT group is postulated to be 11.9%.

9.1.4 Power

The previous rhythm vs. rate control trials were reviewed for the selection of power. The study similar to this study with CV mortality endpoint is AF-CHF, which used a power of 80%.[95] An 80% power was selected.

9.1.5 Cross-over and Loss to Follow-up Rates

We consider cross-over from rate control to catheter ablation-based rhythm control to be a patient randomized to rate control having catheter ablation of AF to control the AF rhythm, and cross-over from catheter ablation-based AF rhythm control to rate control to be a patient randomized to catheter ablation-based AF rhythm control not getting ablation therapy and is then managed by rate control. The cross-over rates are set based on the observation from the recently completed large-scale study (Resynchronization-defibrillation in Ambulatory Heart Failure Trial, RAFT[96]) that we performed with the same investigators and investigation centres. In the RAFT study the crossover rate was low at 1%. This is because of the invasiveness of the intervention (a surgical procedure to implant a pacing lead) similar to this proposed trial (catheter ablation). The rates selected are: 2% (rate to rhythm) and 2% (rhythm to rate). The loss to follow-up rate was set at 2% to reflect the experience in the RAFT study (1%).

9.1.6 Accrual and Follow-up

Based on our experience of the rate and pattern of accrual in the RAFT trial, an accrual over 6 years with a minimal follow-up of 2 years was selected. A minimum follow-up of two years will give a median follow-up of ~54 months. This is an adequate amount of time to observe if the intervention has lasting effect and will allow the intervention to derive any significant benefit on this patient population.

9.1.7 Sample Size Calculation

In order to detect a 30% relative risk reduction in the primary endpoint in the catheter ablation-based AF rhythm control group, at alpha = 0.05 (two-sided) and 80% power, a sample size of 600 patients will be needed (300 in the rate control group and 300 in the catheter ablation-based AF rhythm control group). This calculation assumes an exponential survival with all patients followed to the primary endpoint or termination of the study, and allows for a 2% loss to follow-up in each group and a 2% crossover from each group and an O'Brien Fleming alpha spending function factor (IF) adjustment of 1.02 to adjust the sample size for interim analysis. This treatment comparison is based on the log-rank test. (See Appendix J for details of sample size calculation). A sample size recalculation will be evaluated on an annual basis during the study to accommodate any substantive changes in the overall event rate. Procedures suggested by Betensky[97] and Wittes[98] will be considered and the sample size will only be increased (and not decreased).

9.2.PLANNED RECRUITMENT RATE

The estimated recruitment is 28 patients per month or a little less than one patient per month per centre over 36 months. We plan to have 30 centres participating in this study. The majority of these centres have participated in the RAFT study, which enrolled 1798 patients with an average of 1.5 patients enrolled per month per centre. Only the RAFT centres with good recruitment record are invited to participate in this trial. We have also recruited some other centres based on their previous performance in clinical trials in catheter ablation studies such as the STAR-AF study,[73] which was conducted by one of the principal investigators, Dr. A. Verma. We also plan on compiling a list of other centres from non-Canadian centres that may be included if enrolment is not up to expectation. Dr. V. Essebag will be in charge of this task along with the steering committee members. Only centres with AF ablation experience and volume (>50 ablation per year) will be invited to participate in this study.

9.3.COMPLIANCE

In the rate control strategy, compliance of treatment will be based on the degree of rate control, which will be tracked at each follow-up visit. In the AF-CHF trial 95% of patients had good rate control using the same criteria as that in this trial. In the catheter ablation-based AF rhythm control strategy compliance of treatment is to have catheter ablation performed. Any non-compliance is minimized by: 1) having investigators and patients accepting equipoise of the two treatment strategies, 2) recruiting patients willing to accept the ablation strategy (inclusion criteria 5), and 3) performing the catheter ablation procedure within 2 weeks of randomization.

9.4.LOSS TO FOLLOW UP

We anticipate loss to follow-up will not be more than 2%. In our recently completed RAFT trial involving an invasive procedure, the loss to follow-up is 1%. We believe the dedication of the investigation teams and their expertise with patient care and excellent rapport with patients minimize loss to follow-up to this level.

10. PARTICIPATING CENTRES

This is a multi-centre study with 30 participating centers worldwide (see Appendix L). At each of the clinical centres there will be an EP investigator and a study coordinator who will coordinate study activities at that centre. The individual centres will be responsible for patient

recruitment, completing and transmitting case report forms to the Coordinating Centre, follow-up completion and obtaining information on outcome events.

11. STUDY ANALYSES

11.1. OVERVIEW OF ANALYSES

11.1.1. Analysis Populations

For the purposes of data analysis, three study populations will be considered: *Intent-to-treat (ITT) Population, As-Treated Population and Per-protocol Population.* The ITT population will be used for the main analysis for all primary and secondary research questions, except for the safety analysis (secondary research question 5) where the as-treated population will be used. As a secondary analysis, the analyses will be repeated for the as-treated and per-protocol populations.

11.1.2. Background and Demographic Characteristics

Background and demographic information will be summarized by means of frequency distributions (for categorical variables) and descriptive statistics of mean, standard deviation, minimum, median and maximum (for continuous variables). Background information will include age, sex, LV ejection fraction, NYHA Class, use of ACEI/ARB, use of beta-blockers, diabetes, hypertension, NT-proBNP level, and echocardiographic parameters: LA size, LA volume, LV mass, LV wall thickness, LV ejection fraction. Continuous variables will be tested for baseline comparability between the study groups using the t-test or the Wilcoxon rank-sum test. Categorical variables will be tested for baseline comparability with the chi-square test or Fisher's exact test.

11.1.3. Primary Analysis

The primary analysis (for the primary research question) will compare the time to the primary composite outcome of all-cause mortality or heart failure event *(defined as an admission to a healthcare facility for > 24 hours or clinically significant worsening heart failure leading to an intervention (defined as treatment in an emergency department, a same-day access clinic, or an infusion centre) or unscheduled visits to a healthcare provider for administration of an intravenous diuretic as accepted by FDA and an increase in chronic heart failure therapy (see definition in Appendix O, June 2019)* in the catheter-based AF rhythm control versus rate control groups. The primary outcome will be analyzed using survival analysis techniques. The survival experience (i.e. time-to-primary outcome) in each of the two groups will be summarized using Kaplan-Meier product limit estimates and the nonparametric log-rank test procedure will be used for comparing the survival curves. The hazard ratio (HR) and associated 95 percent confidence interval (95% CI) will be calculated. To adjust for possible effects of covariates on survival, the Cox's proportional hazards model will be used. Underlying assumptions for these statistical procedures will be assessed; in particular, the proportional hazard's assumption will be assessed using graphical and numerical tests.

11.1.4. Secondary Analysis

Catheter-ablation based AF rhythm control vs. rate control groups will be compared on outcomes:

For Secondary Objective A:
Reduce all-cause mortality:
For this analyses, the survival analysis outlined for the primary analysis will be followed. Poisson regression will be used to compare the rates between therapy groups adjusting for possible effects of covariates.

For Secondary Objective B:
Reduce heart failure events*:
For this research question, the therapy groups will be compared on the heart failure event rate (i.e. number of events per unit time alive in the study). Poisson regression will be used to compare the rates between therapy groups adjusting for possible effects of covariates.

For Secondary Objective C:
Improve QOL (as determined by MLWF, EQ5D and AFEQT questionnaires):
For each therapy group, the frequency distribution for MLWHF, each of the domains of the EQ5D, and the AFEQT questionnaire will be tabulated and the mean, standard deviation, median and interquartile range (IQR) calculated. Therapy groups will be compared on these outcomes using the t-test or the Wilcoxon rank-sum test and 95%CI calculated. Repeated measures ANOVA will compare the two therapy groups on changes in health related QOL over time.

For Secondary Objective D:
Improve exercise capacity (as determined by 6 Minute Hall walk distance)

For Secondary Objective E
Reduce NT-proBNP at 1 and 2 years follow-up
For NT-pro BNP in the two groups, changes in these secondary outcomes over time between the two intervention groups will be analyzed using a 2-way repeated measures analysis of variance (ANOVA) with the between factor intervention group and the within factor time (baseline,12 months and annually thereafter).

For Secondary Objective F & G:
In patients with HF, impaired (LVEF ≤ 45%) LV function and high burden AF, to determine if catheter ablation-based rhythm control of AF, as compared with rate control, will reduce all-cause mortality and heart failure events*
In patients with HF, preserved (LVEF >45%) LV function and high burden AF, to determine if catheter ablation-based rhythm control of AF as compared with rate control will reduce all-cause mortality and heart failure events*

A subgroup analysis will be conducted on: (a) the impaired (LVEF≤45%) LV function group; and (b) the preserved (LVEF >45%) LV function group (note randomization was stratified by this variable). For each of these subgroups, the catheter ablation-based AF rhythm control to rate control groups will be compared on all-cause mortality and HF events* using the survival analysis strategy outlined for the primary research question, as well as the Poisson regression comparing event rates outlined for secondary research question 1.

** defined as an admission to a healthcare facility for > 24 hours or clinically significant worsening heart failure leading to an intervention (defined as treatment in an emergency*

department, a same-day access clinic, or an infusion centre) or unscheduled visits to a healthcare provider for administration of an intravenous diuretic as accepted by FDA and an ncrease in chronic heart failure therapy (see definition in Appendix O, June 2019)

For Secondary Objective H:
Be more cost effective:
A cost-utility analysis of catheter-based AF rhythm control vs. rate control groups will be conducted. Analysis will take the form of a cost utility analysis with cost effectiveness assessed in terms of the incremental cost per quality life year. A short term analysis will incorporate data on resource use and patients utility values for the period from initiation of treatment to 24 month; the minimum period of follow up within the clinical trial. Resource use will be assessed through review of patient charts and patient utility values will be derived using the EQ5D. Long-term analysis will use a Markov model developed for this study, which will estimate long-term costs and quality adjusted life years (QALYs) for all comparators. Uncertainty within the analyses will be assessed through bootstrap and Monte Carlo simulation techniques as well as Bayesian value of information analyses. A detailed description of the analytical approach is contained in Appendix K.

11.1.5. Safety analysis

A safety analysis of catheter ablation-based AF rhythm control compared to data based on the worldwide survey[61] will be conducted. Safety will be evaluated by documenting all events (analyzed individually and in entirety) of thromboembolism, symptomatic PV stenosis, atrio-esophageal fistula, pericardial effusion requiring pericardiocentesis and major bleeding requiring blood transfusion, amiodarone induced thyroid, pulmonary and other toxicity in the catheter-based AF rhythm control. In patients with CRT/ICD devices, any disruption of these devices requiring intervention will also be recorded. Descriptive statistics (frequency distributions, numerical descriptors) and 95% CIs will be calculated. The occurrence of each of these events will be compared to that in the worldwide survey using the Wilcox on rank-sum test. The as-treated population will be the main analysis population for this safety evaluation.

Tertiary Objectives:
A) Improve LV function and remodeling (LVESVi) at 1 Year and 2 Year Follow up. Reverse remodeling between the two groups will be assessed, i.e. the reduction of LVESVi from baseline to 12 months and annually thereafter, The mean difference (MD) and associated 95 percent confidence interval (95% CI) will be calculated.

B) Reduce AF burden at 1 year and 2 year follow up: Logistic regression models will be used to evaluate the occurrence of all-cause mortality and HF events with the change in AF burden before and after catheter ablation, adjusting for baseline covariates. The natural history of AF burden over time (at 6, 12, 18 and 24 months &/or at 6 months visits subsequently) in the rate control arm will be assessed using a mixed methods repeated measures (MMRM) analysis. Growth curve analysis will also be conducted. That is, for each patient, the AF burden will be regressed against time to characterize the change in AF burden over time. Clinical outcomes will be assessed with respect to burden by comparing the various regression parameters between clinical outcome groups (outcome yes vs. no) using the t-test or the Wilcoxon rank-sum test and 95% confidence interval (CI). The clinical outcome groups will also be compared using multiple

regression models controlling for baseline covariates. Finally, logistic regression models will be used to assess the occurrence of clinical outcomes with the change in AF burden adjusting for baseline covariates.

C) Reduce the total number of heart failure events*

D) Decrease the total number of CV events (including AV node ablation, device admissions)

** Heart failure events (defined as an admission to a healthcare facility for > 24 hours or clinically significant worsening heart failure leading to an intervention (defined as treatment in an emergency department, a same-day access clinic, or an infusion centre) or unscheduled visits to a healthcare provider for administration of an intravenous diuretic as accepted by FDA and an increase in chronic heart failure therapy (see definition in Appendix O, June 2019)*

11.1.6. Missing Data

Missing data is considered to be missing at random (MAR) and mixed methods repeated measures (MMRM) and multiple imputation (MI) techniques will be used for handling missing data. In particular, for continuous outcomes at multiple time points MMRM will be used.

11.2. FREQUENCY OF ANALYSES

One interim analysis is planned when 33% of patients enrolled have been followed for a minimum of 1 year. This will occur approximately after 2 ½ years of the 3-year patient recruitment period. A final analysis will be performed at the conclusion of the trial. An O'Brien Fleming alpha spending function was used to adjust the sample size for interim analysis.

11.3. PLANNED SUBGROUP ANALYSES

Subgroup analyses based on patient characteristics will be undertaken, primarily for sensitivity analyses to assess the robustness of the results, as well as for exploratory purposes for hypothesis generation. In particular, planned subgroups include: impaired (LVEF≤45%) vs. preserved (LVEF>45%) LV function; and AF pattern: paroxysmal vs. persistent

12. ETHICS REVIEW

The Investigators at each of the participating clinical centres will ensure that this study is conducted in accordance with the principles of the Declaration of Helsinki. They will ensure that this study is conducted in full conformity with relevant regulations and with the ICH Guidelines for Good Clinical Practice (CPMP/ICH/135/95) July 1996.

12.1. INSTITUTIONAL REVIEW BOARD/ETHICS COMMITTEE

A copy of this protocol, including protocol amendments, all versions of informed consent forms, and questionnaires will be reviewed and approved by the Research Ethics Board (REB) or Institutional Review Board (IRB) of each of the participating clinical centres. The investigator will notify the IRB/REB of serious adverse event and protocol deviations related to patient safety.

12.2. INFORMED CONSENT

Before study inclusion, patients will be given detailed oral and written information about the principles and the protocol objectives of the study. The consent process will follow all ICH GCP guidelines as per section 4.8 Informed consent of trial patients. Patient information will be

handled at all times in accordance with appropriate confidentiality standards and all applicable data protection and privacy laws.

12.3. PARTICIPANT CONFIDENTIALITY

All patient related information including Case Report Forms, evaluation forms, reports, questionnaires, etc. will be kept strictly confidential. All records will be kept in a secure, locked location and only research staff will have access to the records. Patients will be identified only by means of a coded number specific to each patient. All computerized databases will identify patients by numeric codes only, and will be password protected.

13. STUDY ORGANIZATION

13.1. COORDINATING CENTRE

The Cardiovascular Research Method Centre (CRMC) at the University of Ottawa Heart Institute under the direction of Dr. Wells will coordinate the day-to-day management of the trial. Central randomization of patients and data collection will be implemented using a web-based system, and data will be managed in and analyzed using SAS following the procedures developed for trials such as RAFT.

13.2. COMMITTEES

13.2.1. Executive and Steering Committee

The applicant and co-applicants form the Steering Committee for this trial. The Principal applicant, Dr. Tang, will serve as principal spokesperson for the study, chair the Committee and maintain communication within the study. Dr. Wells has extensive expertise and experience in the design and analysis of large multicentre clinical trials and will be the head of the coordinating centre for this trial. Dr. Talajic has been the leader of many clinical trials including the AF-CHF trial. He will be advising on the conduct of the trial from an AF perspective. Dr. Verma is well published in catheter ablation of AF and is the PI of several ablation trials. He will be advising on the ablation perspective. Dr. Parkash is a clinician-scientist and recipient of a CIHR clinical trial mentorship award. Dr. Rouleau is a world leader in HF research. He will be advising and monitoring HF management in the trial. Dr. Coyle is an experienced health economist. He will supervise the conduct of the economic analysis for this trial. Dr. Healey, a clinician-scientist with extensive clinical trial experience, and Dr. Newton, a HF clinician-scientist will co-chair the clinical event adjudication committee. Dr. Essebag is a CIHR clinician-scientist with clinical trial expertise; he will serve as recruitment coordinator overseeing the recruitment progress, with ongoing communication with each centre and with communication of potential expansion centres if necessary. Dr. Macle and Skanes are interventional electrophysiologists with expertise and research records on catheter ablation. They will serve as reviewers of ablation technique used for the trials and monitor the records (maps and ablation procedure data forms) of patients in the catheter ablation-based rhythm control arm to ensure the patients are receiving appropriate ablation treatment. Dr. Birnie is a clinician-scientist with clinical trial expertise. He will be helping Dr. Wells to monitor the quality of the coordinating centre and assess in reviewing data query and assurance that ongoing patient care is maintained by monitoring medication and other ongoing treatment.

13.2.2. Data Monitoring Committee

A data monitoring committee will be set up. A three person DMC will consist of an electrophysiologist, a HF specialist and a biostatistician with trial expertise. A charter governing the operations of the DMC will be developed in conjunction with DMC to determine specific procedures such as the frequency of reports/meetings and content of the safety analyses reports.

14. DATA HANDLING

14.1. DATA MANAGEMENT RESPONSIBILITIES

Data management and randomization will be coordinated by the Cardiovascular Research Methods Centre (CRMC) of the University of Ottawa Heart Institute. More specifically, the CRMC will be involved in the following:

- Implementing the web-based randomization schedules;
- Developing online case record forms (baseline visit, follow-up visits, study exit visit, event forms, protocol deviation forms);
- Designing and implementing databases;
- Management and monitoring of data and data flow;
- Coordinating the electronic data entry;
- Generating standard and study specific statistical reports;

The study will be conducted in accordance with the current approved protocol, ICH GCP, relevant regulations and standard operating procedures.

The CRMC has standard operating procedures (SOPs) to help ensure good clinical practice and good laboratory practice related to the study methods, data management and integrity. Detailed operating manuals and data management manuals will be provided to each study centre

14.2. DATA CAPTURE METHODS

The CRMC's web based electronic data capture system, will be implemented, providing the study with its own dedicated and secure website. This website is tailored to the study specific workflow, which enables easy questionnaire management for both research staff and study participants. As part of the data management system, randomization of study participants will be conducted using a flexible web based randomization system to perform the planned stratified and block randomization.

15. SOURCE DOCUMENTS

Each participating centre must maintain appropriate medical and research records for this trial and regulatory/institutional requirements for the protection of confidentiality of study patients. The Principal Investigator is responsible for assuring that the data collected are complete, accurate, and recorded in a timely manner.

Study data will be collected on study specific case report forms and questionnaires will be filled in during baseline and follow-up visits. Data will be entered into the web based system and stored electronically at the CRMC. Source documents and all forms will be stored at the individual study centres responsible for collecting the data. All Study information including

paper files and computer software must be kept by the sponsor and at each participating study centre in a secure area, accessible only to study qualified personnel, for a maximum of 25 years.

Each participating centre must keep, in its files, a master list of the contents stored, whether or not the files are stored at the site or off-site. All study material must have the ability to be recalled in the event of a future audit or query.

The study specific material to be stored includes but not limited to the following:

a) Centre study operations manual
b) All CRFs
c) All patients source documentation
d) All study related communications
e) Any other study related material

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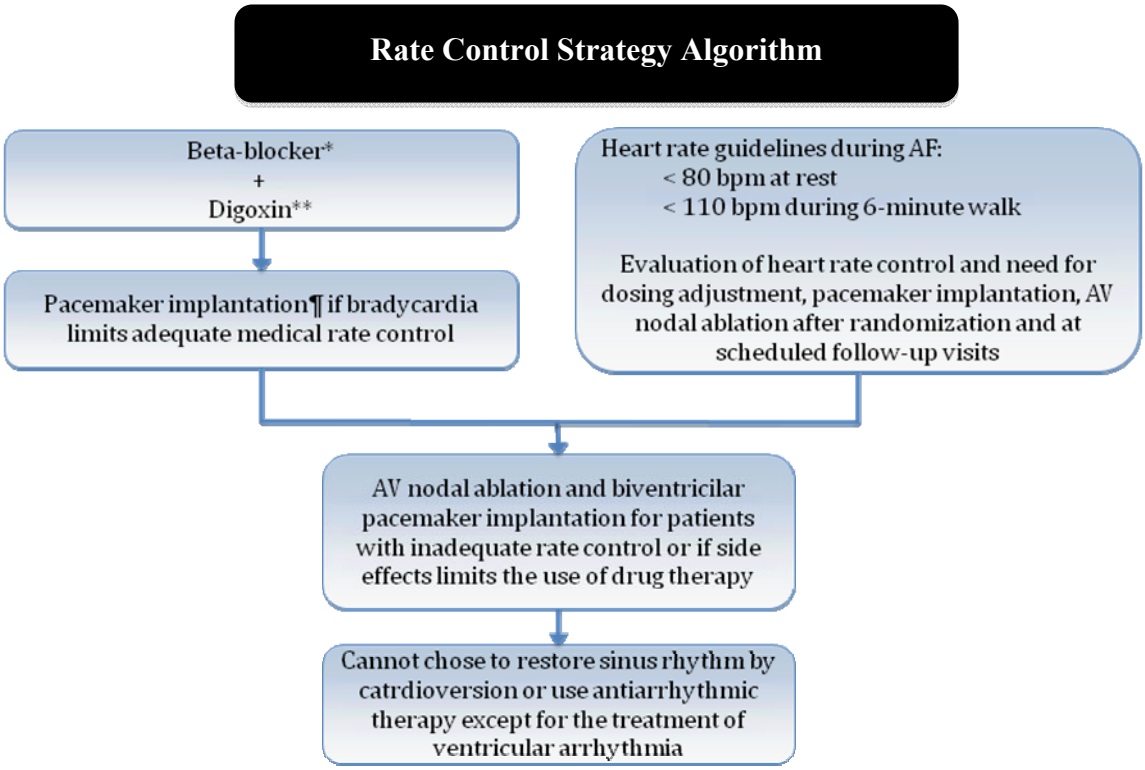
17. APPENDIX

Appendix A. Schedule of Events

Evaluation	Screening	Baseline/ Randomization	FUV #1 (2 months)	FUV #2 (4 months)	FUV #3 (6 month and Q6 months)	Exit Visit (end of study)
Assessment of inclusion/exclusion criteria	X					
Informed Consent	X					
Optimal therapy for HF as per guidelines	X					
Clarification of amiodarone and anti-coagulation status	X					
Demographics	X					
Basic Physical Exam		X	X	X	X	X
Medical History/Cardiovascular History		X				
Medication Assessment		X	X	X	X	X
Blood Chemistry Profile (from recent clinical visit)		X			X (12,and Q 6 M after)	X
Echocardiogram (standard of care_DICOM)		X			X (12 M & Annually)	
12-lead ECG		X	X	X	X	X
NT- proBNP blood test	X	X (if not done at screening)			X (12 M & Annually)	
6 MHW		X	X	X	X	X
QOL questionnaires		X			X(12,and Q 6 M after	X
14 Day Continuous ECG Monitoring		X			X (6 M, 12 M, 18 M, 24 M &/or Q6 M visit)	

Appendix B. Rate Control Strategy Algorithm



* Beta-blocker:	Metoprolol - starting 6.25 mg - 25 mg twice a day, maximum 50 - 100 mg twice a day. Carvedilol - starting 3.125 mg twice a day, maximum 25 -50 mg twice a day. Bisoprolol – starting 1.25 mg/day, maximum 10 mg/day.
** Digoxin:	0.125 to 0.25 mg/day according to age, renal function and concomitant medication.
¶Pacemaker:	Recommend biventricular pacemaker when AV nodal ablation is to be used to control heart rate.
ICD and CRT:	Recommend in the case of impaired LV function as per ACC/AHA guidelines.

Appendix C. Catheter Ablation based-Rhythm Control Strategy Algorithm

Catheter Ablation-based Rhythm Control Strategy Algorithm

Pre-Ablation:
Anticoagulation with INR > 2 for > 4 weeks
Amiodarone stopped > 6 weeks
Other antiarrhythmic drug stopped > 5 half-life
CT/CMR image at the discretion of the investigator
Pre-procedure TEE optional

Ablation Procedure:
Conscious sedation or general anesthesia
Esophageal temperature monitoring optional
Intra-cardiac ultrasound monitoring optional
3-D map of LA and PV with Carto or NavX
After trans-septal puncture, IV heparin to keep ACT>250 sec
Use saline irrigated ablation catheter with the following RF settings:
Catheter temperature 43°C,
Power ≤ 25 Watt for posterior LA, otherwise ≤ 35 Watts

Lesion set:
PV antral ablation with confirmation of entrance and exit block and one of the following:
1) 1. LA roof and mitral isthmus line with confirmation of bidirectional conduction block
2) 2. LA roof and ablation targeting LA complex fractionated electrogram
3) 3. Mitral isthmus and ablation targeting LA complex fractionated electrogram
4) 4. Ablation targeting LA complex fractionated electrogram

Any spontaneous or induce RA or LA flutter/tachycardia is to be mapped and ablated
Cardioversion to restore sinus rhythm if AF/flutter/tachycardia persisted
Check for PV entrance and exit block and line bidirectional conduction block

Post-Ablation:
Hospital observation up to 24 hours
Anticoagulation bridging if applicable with LMWH 24 hours post ablation for 5 days
Oral anticoagulation with INR 2-3 indefinitely
Antiarrhythmic drug* for 4-6 weeks post ablation optional
Proton pump inhibitor for 4-6 weeks

AF recurrence after ablation:
For AF/flutter/tachycardia > 4 weeks post ablation a repeat ablation procedure is highly recommended.
Repeat ablation procedure shall be the same as the first ablation procedure.

Antiarrhythmic drug use:
Antiarrhythmic drug* can be used for 4-6 weeks post ablation to reduce post-ablation atrial arrhythmia.
Long term antiarrhythmic drug* is not to be used routinely
Long term antiarrhythmic drugs* can be used as adjunctive therapy for AF suppression after at least two ablation procedures.

*Antiarrhythmic drugs:

Amiodarone or Dofetilide can be used in patients with impaired LV function; Amiodarone or Dofetilide, can be used in patients with preserved LV function. Amiodarone oral loading 400 mg twice a day or three times a day for 10 days then 200 mg per day
Dofetilide 500 mg twice a day when eGFR >60 ml/min; 250 mg twice a day when eGFR is 40-60 ml/min; 125 mg twice a day when eGFR < 20 ml/min

Appendix C1. ST JUDE VELOCITY CFE MAPPING ALGORITHM

Once in AF, CFE mapping using the automated algorithm will be performed in the LA, CS, and RA (if needed).

EGMs should be obtained during AF by mapping with the circular mapping catheter. In areas were the circular mapping catheter cannot obtain good atrial contact, mapping may be supplemented using the 4 mm tip ablation catheter. Bipolar recordings are to be filtered at 30-300 Hz (default value).

The detailed technique for mapping/ablating CFE using the automated algorithm has been described and validated previously. In brief, the algorithm measures the time between multiple, discrete deflections (-dV/dT) in a local AF electrogram (EGM) recording over a specified length of time (5 sec) and then averages these inter-deflection time intervals to calculate a mean cycle length (CL) of the local EGM during AF. This mean CL is then projected onto the LA anatomical shell as a color-coded display. The shorter the CL, the more rapid and fractionated the local EGM. Specifically for this study, regions with a mean CL of less than 120 ms will be defined as "CFE" based on previously published data[1].

The recommendations and settings for EnSite Complex Fractionated Electrograms Algorithm – CFE is reported in Table 4.

At the start of the procedure, the baseline signal noise level should be determined and the P-P Sensitivity limit is to be set just above the noise level (typically 0.03-0.05 mV) to avoid noise detection while allowing detection of low amplitude CFE (often <0.5 mV).

Selectable peak to peak EGM amplitude, EGM width, and post-EGM refractory period are defined to assist in algorithm deflection detection

Width Value and Refractory Value are typically set at 15-20 ms and 35-45 ms respectively to avoid detection of far-field EGMs and to avoid double-counting individual EGM deflections.

To avoid including signals from bipoles that are internal in the LA, the Interpolation Value of the algorithm should be adjusted (no more than 10 mm) to include only those signals obtained from bipoles with good atrial shell contact.CFE sites defined by the algorithm (CL < 120 ms) will be targeted for ablation. Regions with the shortest CL should be targeted first, followed by longer CL regions (up to 120 ms). Ablation at a CFE site shall be continued until the local EGM is completely eliminated which typically requires 20-60 sec of RF application.

During ablation of CFE sites, the mean atrial fibrillation cycle length (AFCL) and AF regularity should be measured from a selected CS recording. The CS recording with the shortest average CL is recommended, and the same recording should be used for pre- and post-ablation comparisons. AFCL is determined by counting the number of discrete atrial EGMs over a 15 sec recording (x) and dividing 15000 by x. The CS recording should also be examined to look for regularization of AF to atrial flutter or tachycardia during CFE ablation. Termination of AF to a regular atrial rhythm or sinus rhythm during CFE ablation should be recorded. No intravenous antiarrhythmics should be used during CFE ablation to change AFCL or help regularize/terminate AF.

The endpoint for CFE ablation is**:**

Complete elimination of all CFE regions identified by the algorithm in the LA, CS and RA, or

AF termination.

Initially, all CFE sites in the LA and CS should be targeted. If AF does not terminate into sinus or another regularized arrhythmia, CFE in the RA should be mapped and ablated.

If AF still does not terminate, sinus rhythm may be restored by electrical cardioversion

If AF terminates to sinus rhythm, any remaining unablated CFE sites do not need to be ablated.

If AF terminates to an atrial flutter/tachycardia, all remaining CFE sites should be ablated.

If AF terminates to an atrial flutter or tachycardia, and the required randomization ablation strategy has been completed, then the atrial flutter and tachycardia may be ablated or electrically cardioverted at the discretion of the investigator. The location and nature of the additional lesions and/or the cardioversion should be recorded and documented.

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Table 4 - Recommendations and Settings for EnSite CFE Algorithm

As CFE mapping catheter use the circular mapping catheter or ablation catheter in regions where the circular mapping catheter has poor contact. The circular mapping catheter is preferable. Its electrodes size and electrodes spacing allow increasing the signal quality.		
Assess the baseline noise using the callipers of the DX Landmarking Tools		
Parameter	**Value**	**Parameter definition**
P-P Sensitivity	0.03-0.05 mV (Just above the baseline noise)	The P-P Sensitivity control is a minimum peak-to-peak voltage required for the detection algorithm to operate. Incoming signals must be larger than the P-P Sensitivity in order to be considered activation by the system.
Width value	15-20 ms	The Width slider controls the minimum complex width to consider for activation. As CFE maps always use -dVdt detection type, this parameter indicates the width of the most negative slope. This setting will avoid detection of far-field smooth deflection.
Refractory value	35-45 ms	The Refractory slider controls the minimum amount of time between detections, in order to avoid over counting a single EGM with multiple components.
EGM Segment Length	min 5 s	The Segment Length indicates the total recording duration at each point.
Interpolation value	4-8 mm	The Interpolation slider controls the minimum distance between surface points necessary for the system to interpolate color.
Interior Projection Exterior Projection	4-8 mm	Interior and Exterior Projection are projection sliders that control the Maximum/minimum distance that a 3D Point can project to a location on the interior geometry surface. This setting will avoid collection of EGMs from electrodes that are not in good contact with map shell
Auto-color	ON	The Auto Color toggle controls whether the system automatically controls the pointers on the color bar during DX Landmarking. If Auto Color is enabled, the pointers will adjust to the minimum and maximum data values for all points in the current map.
Set the color-slider so that the orange-red transition occurs around 120 ms. All regions < 120 msec will be considered “CFE” region. Those region will appear red or white.		
Confirm accuracy of regions labeled as “CFE” by checking EGMs visually		
Target all red-white regions for ablation. This will often require several lesions over “islands” of CFE throughout the atrium. Try to target white spots (the shortest CL) first.		
If CFE ablation in the LA and CS do not terminate AF, map and ablate CFE in the RA.		

Appendix C2. CFAE MAPPING ALGORITHM:

At each mapping site, a 2.5-second window of bipolar EGMs will be analyzed online by programmable CFAE Software Module Version 9.7 that provides online automated identification and electroanatomical display of CFE.

The extent and repetitiveness of EGM fractionation are determined by algorithms described in detail elsewhere 28, 30. In brief, a programmable lower threshold for EGM identification is set to exclude noise (±0.05 mV). Voltage peaks greater than this threshold but less than an upper threshold (±0.15 mV) are then identified.

The intervals between successive peaks falling within the voltage window and within a programmable duration (60–120 ms) are then counted and summed over the 2.5 second sampling window, designated the interval confidence level (ICL). ICL can be depicted as a color-coded gradient map on the LA and CS shells (fill threshold 10 mm). All sites with higher ICL (> 7) reflect more repetitive CFE and will ultimately be targeted for generalized CFAE ablation.

TIPS AND TRICKS FOR CFAE and CFR MODULES IN CARTO:

It is important to understand that automated modules are meant to assist the operator in identifying areas of interest. However, like any automated tool, the information provided must be verified and calibrated before each case.

In the CFAE module, there is a voltage range which specifies a lower limit (default = 0.03 mV) and an upper range (0.15 mV). This means that no signals below 0.03 mV will be annotated (to avoid noise detection) and no signal above 0.15 mV will be annotated (since CFAE are supposed to be low voltage signals). However, the lower limit may need to be adjusted depending on the noise level of your lab. As a check, you can place the ablation catheter in the middle of the LA (no wall contact). Measure the voltage on the recording. Ideally, it should be zero (in a noiseless lab), but if it is above 0.03 mV, you may need to increase the lower limit so as to filter out this noise. The upper limit is typically fine as is, however, if you have a "young, healthy" atrium, where the voltages are very high throughout, even the CFAE can have a higher voltage. Thus, you may need to increase the upper voltage limit (up to 0.30 mV) in order to accommodate this.

In the CFAE module, there is also a minimum (default 50 ms) and a maximum (default 100 ms) duration identified for the intervals. Remember, the ICL is the number of short intervals between successive low-amplitude deflections. The more the number of short intervals, the more "fractionated" the signal. Any interval less than 50 ms will not be identified as a unique interval (to avoid double-counting a single electrogram) and no interval greater than 100 ms will be identified as a unique interval (to avoid long, isoelectric pauses between signals). In the paper by

Wilber et al, JCE 2008, the default values set were a lower limit of 60 ms and an upper limit of 120 ms. For most cases, these settings do not make a tremendous difference. However, in patients who start off with a longer cycle length AF (almost a cross between AF and AFL or "flitter"), the upper limit may need to be extended beyond 100 ms (up to 150 ms).

Here's how you can easily determine where the most optimal settings should be:

1. First place your catheter in the middle of the LA (no wall contact) to measure the noise level and adjust the lower voltage limit accordingly

2. Quickly look at the voltages of the signals in the LA. If they are very robust, you may need to adjust the upper voltage limit

3. Quickly look at the cycle length of the AF. If it is more of a "flitter" with a cycle length >190 ms, then you may need to adjust the upper duration limit

4. To decide how much to adjust the voltage and duration limits, place your catheter in a position where you obviously have CFAE or continuous fractionation by visual inspection. Acquire a point. If it gives you a value that seems to correlate with your visual inspection, then the algorithm is working well. If not, then adjust the limits until the value is in line with what you are seeing. Think of this as a calibration test.

The other issue that comes up is the amount of LA that is identified as CFAE:

1. The whole LA has been labelled as CFAE. What do I do?

First, check that your ICL limit has been established at 7 (not 5). Second, do your calibration check as outlined in the last section. If everything seems to be working OK, then perhaps your atrium does have a lot of CFAE. Here's how I handle this - adjust your ICL limit to 9 or 10 to highlight only those VERY fractionated regions. Start ablating only these areas. AF may terminate as a result of this. If not, then gradually extend your ablation lesions by lowering the ICL limit towards 7.

Appendix D. QOL Instructions

QUALITY OF LIFE QUESTIONNAIRE FORM INSTRUCTIONS

For the purpose of obtaining valid and reliable data, it is important to read and adhere to the guidelines of administering the following quality of life questionnaires: **1) Minnesota Living with Heart Failure** (MLWHF) and **2) EQ5D (& EQVAS) Questionnaire** provided below**.**

The way in which a questionnaire is administered to a study participant can affect the validity of the responses. The individual administering the questionnaire plays a critical role in the process of data collection.

IMPORTANT: Please send home a blank **copy** of questionnaires (total 3 pages) for patients as a reference guide for patients to use when they are contacted for their RAFT-AF follow up visits.

MINNESOTA LIVING WITH HEART FAILURE (MLWHF)

In this study, the MLWHF QOL questionnaire will be self-administered, but it can be administered in an interview format if necessary.

Introduce the questionnaire to the study participants by telling them that the questionnaire contains questions about their general well-being and that we are asking them to complete this questionnaire because we are interested in knowing how having heart failure may have affected their daily life.

When introducing the MLWHF questionnaire, explain to the patients that their responses to the measures will be kept completely confidential, and no one but the research staff will have access to their names. Data will be entered into the computer by RAFT-AF study numbers rather than names. Results will be calculated using large groups of patients, and not individuals. If results are published, no names or other identifying characteristics will ever be used.

Prior to each administration of the questionnaire, it is important that you review the study protocol and questionnaire to refresh your memory as to the correct procedures to follow. This is particularly important in clinic; where more than one clinic staff member will be administering the questionnaire.
You should determine if the participant is able to complete the questionnaire without assistance. It is possible that you will encounter participants with vision problems, language problems or physical conditions which will make it difficult for them to complete the questionnaires their own.

If you suspect that a participant is unable to read, *while avoiding embarrassment to the participant,* you may say: “Sometimes people prefer to have the questionnaire read to them. Would you like me to read these questions to you? ” If the answer is yes, read the questions and response categories verbatim and in the order they appear in the questionnaire.

Family members or friends of the participant should not be present when the patient is completing the questionnaire. Oftentimes, family members will offer to help participants complete the questionnaire that will influence the validity of the data.

Put the patient in a comfortable and private place, free from interruption or distractions.

You should be readily accessible to answer questions while the questionnaire is being completed.

In answering questions, you must remain neutral. Keep explanation to a minimum. Don't interpret questions. You may, for example, read a question, define a word, indicate where the answer is to be marked, but you should not paraphrase questions unless it is absolutely necessary. In general, most of the questions can be handled by reminding the patients to follow the directions on the questionnaire, or simply by rereading the statements to them. Under no circumstances should you help the participant decide how to mark a questionnaire item.

Have the patient complete the questionnaire in one sitting.

Ask the patient to take their time and give enough thought to each question on the questionnaire, remind them that they should answer the question with the response that they believe is more true for them at the present time. The choice is theirs as to how to respond to questions, and assure them that there are no right or wrong answers to these questions.

Immediately after the survey is completed, identify missing information and/or other problems, request that all questionnaire items be completed. If a respondent replies that none of the choices is correct, suggest that the choice that comes closest be selected. If the respondent still refuses, note this on the questionnaire and accept the participant's refusal without comment.

Always remember to thank the participant for their time and interest in completing the questionnaire. Escort the participant back to their family or the waiting room, if necessary.

EQ5D (& EQVAS)

The respondent is asked to indicate his/her health state by ticking (or placing a cross) in the box against the most appropriate statement in each of the 5 dimensions. This decision results in a one-digit number expressing the level selected for that dimension. The digits for five dimensions can be combined in a five-digit number describing the respondent's health state. It should be noted that the numerals 1-3 have no arithmetic properties and should not be used as a cardinal score.

Although self-explanatory instructions are provided within the text, the following guidelines may be helpful.

A respondent may sometimes find that the number of levels is too limited. For example, for the mobility question, a respondent in a wheelchair is not 'confined to bed', but he/she may find 'some problems in walking about' appears to under-estimate their level of difficulty. If an administrator is present he/she should stress the instruction: 'please indicate which statements *best* describe your own health state today'. It is the respondent's personal evaluation that is required and on no account should a prompt be given.

The **EQ VAS** generates a self-rating of health-related quality of life. It should be used with the 5-digit health state classification to build a composite picture of the respondent's health status. The respondent rates his/her health state by drawing a line from the box marked "Your health state today" to the appropriate point on the EQ VAS.

Sometimes, respondents tend to rate their health state by placing a mark on the thermometer instead of drawing a line. There is no reason why this could not be interpreted as a valid response.

If the line does not cross the thermometer, the value horizontally opposite where the line stops should be taken and not where it would be if hypothetically extended. It is important to ensure that the respondent is not prompted in any way by the administrator and that it is the respondent's own rating of health-related quality of life that is being recorded.

The MLWHF and EQ5D questionnaires are available and validated in multiple languages. We have used the English, French, German, Danish, Dutch, Turkish, and Spanish versions in our previous studies

Appendix E. MINNESOTA LIVING WITH HEART FAILURE (MLWHF)

SECTION 5: QUALITY OF LIFE QUESTIONNAIRE

(Required at all scheduled follow up visits)

These questions concern how your heart failure (heart condition) has prevented you from living as you wanted during the last month. These items listed below describe different ways some people are affected. IF you are sure an item does not apply to you or is not related to your heart failure, then circle 0 (No) and go on to the next item. If an item does apply to you, circle the number rating how much it prevented you from living as you wanted. Remember to think about *ONLY THE LAST MONTH*.

Did your heart failure prevent you from living as you wanted during the last month by:

	No	Very Little →				Very Much
1. Causing swelling in your ankles, legs, etc.?	0	1	2	3	4	5
2. Making the work around your house or yard difficult?	0	1	2	3	4	5
3. Making your relating to or doing things with your friends or family difficult?	0	1	2	3	4	5
4. Making you sit or lie down to rest during the day?	0	1	2	3	4	5
5. Making you tired, fatigued, or low on energy?	0	1	2	3	4	5
6. Making your working to earn a living difficult?	0	1	2	3	4	5
7. Making your walking about or climbing stairs difficult?	0	1	2	3	4	5
8. Making you short of breath?	0	1	2	3	4	5
9. Making your sleeping well at night difficult?	0	1	2	3	4	5
10. Making you eat less of the foods you like?	0	1	2	3	4	5
11. Making your going places away from home difficult?	0	1	2	3	4	5
12. Making your sexual activities difficult	0	1	2	3	4	5
13. Making your recreational past times, sports, or hobbies difficult?	0	1	2	3	4	5
14. Making it difficult for you to concentrate or remember things?	0	1	2	3	4	5
15. Giving you side effects from medications?	0	1	2	3	4	5
16. Making you worry?	0	1	2	3	4	5
17. Making you feel depressed?	0	1	2	3	4	5
18. Costing you money for medical care?	0	1	2	3	4	5
19. Making you feel a loss of self-control in your life?	0	1	2	3	4	5
20. Making you stay in a hospital?	0	1	2	3	4	5
21. Making you feel you are a burden to your family and friends?	0	1	2	3	4	5

Appendix F. EQ5D Questionnaire

SECTION 6: EQ5D QUESTIONNAIRE

By placing a check-mark in one BOX in each group below, please indicate which statements best describe your own state of health **today.**

MOBILITY	*Place a check-mark in one BOX*
I have no problems in walking about	☐
I have some problems in walking about	☐
I am confined to bed	☐

SELF- CARE	*Place a check-mark in one BOX*
I have no problems with self-care	☐
I have some problems washing or dressing myself	☐
I am unable to wash or dress myself	☐

USUAL ACTIVITIES *(e.g. work, study, housework, family or leisure activities)*	*Place a check mark in one BOX*
I have no problems with performing my usual activities	☐
I have some problems with performing my usual activities	☐
I am unable to perform my usual activities	☐

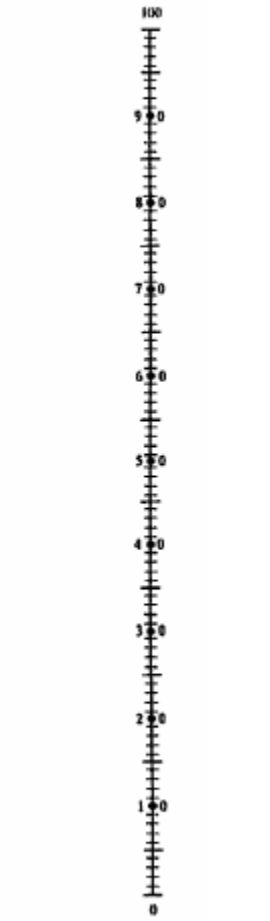
PAIN/DISCOMFORT	*Place a check-mark in one BOX*
I have no pain or discomfort	☐
I have moderate pain or discomfort	☐
I have extreme pain or discomfort	☐

ANXIETY/DEPRESSION	*Place a check-mark in one BOX*
I am not anxious or depressed	☐
I am moderately anxious or depressed	☐
I am extremely anxious or depressed	☐

To help people say how good or bad their state of health is, we have drawn a scale (rather like a thermometer)on which the best state you can imagine is marked 100 and the worst state you can imagine is marked 0.

We would like you to indicate on this scale how good or bad your own health is today, in your opinion. Please do this by drawing a line from the box below to whichever point on the scale indicates how good or bad your state of health is today.

Best imaginable state of health



Your own state of health today

Worst imaginable state of health

Appendix G. The Atrial Fibrillation Effect on QualiTy-of –life (AFEQT)

Atrial Fibrillation Effect on QualiTy-of-life (AFEQT) Questionnaire

Section 1.
Occurrence of atrial fibrillation

Are you currently in atrial fibrillation? ☐ Yes ☐ No

If **No**, when was the last time you were aware of having had an episode of atrial fibrillation?
(Please check one answer which best describes your situation)

__ earlier today
__ within the past week
__ within the past month
__ 1 month to 1 year ago
__ More than 1 year ago
__ I was never aware of having atrial fibrillation

Section 2.
The following questions refer to how atrial fibrillation affects your quality of life.

On a scale of 1 to 7, over the past 4 weeks, as a result of your atrial fibrillation, how much were you bothered by:
(Please circle one number which best describes your situation)

	Not at all bothered Or I did not have this symptom	Hardly bothered	A little bothered	Moderately bothered	Quite a bit bothered	Very bothered	Extremely bothered
1. Palpitations: Heart fluttering, skipping or racing	1	2	3	4	5	6	7
2. Irregular heart beat	1	2	3	4	5	6	7
3. A pause in heart activity	1	2	3	4	5	6	7
4. Lightheadedness or dizziness	1	2	3	4	5	6	7

On a scale of 1 to 7, over the past 4 weeks, have you been limited by your atrial fibrillation in your:
(Please circle one number which best describes your situation)

	Not at all limited	Hardly limited	A little limited	Moderately limited	Quite a bit limited	Very limited	Extremely limited
5. Ability to have recreational pastimes, sports, and hobbies	1	2	3	4	5	6	7
6. Ability to have a relationship and do things with friends and family	1	2	3	4	5	6	7

On a scale of 1 to 7, over the past 4 weeks, as a result of your atrial fibrillation, how much difficulty have you had in:
(Please circle one number which best describes your situation):

	No difficulty at all	Hardly any difficulty	A little difficulty	Moderate difficulty	Quite a bit of difficulty	A lot of difficulty	Extreme difficulty
7. Doing any activity because you felt tired, fatigued, or low on energy	1	2	3	4	5	6	7
8. Doing physical activity because of shortness of breath	1	2	3	4	5	6	7
9. Exercising	1	2	3	4	5	6	7
10. Walking briskly	1	2	3	4	5	6	7
11. Walking briskly uphill or carrying groceries or other items, up a flight of stairs without stopping	1	2	3	4	5	6	7
12. Doing vigorous activities such as lifting or moving heavy furniture, running, or participating in strenuous sports like tennis or racquetball	1	2	3	4	5	6	7

On a scale of 1 to 7, over the past 4 weeks as a result of your atrial fibrillation, how much did the feelings below bother you?
(Please circle one number which best describes your situation)

	Not at all Bothered	Hardly bothered	A little bothered	Moderately bothered	Quite a bit bothered	Very bothered	Extremely bothered
13. Feeling worried or anxious that your atrial fibrillation can start anytime	1	2	3	4	5	6	7
14. Feeling worried that atrial fibrillation may worsen other medical conditions in the long run	1	2	3	4	5	6	7

Appendix H. Canadian Cardiovascular Society Severity in Atrial Fibrillation (CCS-SAF)

Canadian Cardiovascular Society
Severity of Atrial Fibrillation (SAF) Scale

Step 1 – *S*ymptoms

Identify the presence of the following symptoms:

- Palpitation
- Dyspnea
- Dizziness, presyncope, or syncope
- Chest pain
- Weakness or fatigue

Step 2 – *A*ssociation

Is AF, when present, associated with the above-listed symptoms (A-E)?

For example: Ascertain if any of the above symptoms are present during AF and likely caused by AF (as opposed to some other cause).

Step 3 – *F*unctionality

Determine if the symptoms associated with AF (or the treatment of AF) affect the patient's functionality (subjective quality of life).

CCS-SAF Class Definitions

Class 0

Asymptomatic with respect to AF

Class 1

Symptoms attributable to AF have ***minimal*** effect on patient's general QOL.

- minimal and/or infrequent symptoms, or
- single episode of AF without syncope or heart failure

Class 2

Symptoms attributable to AF have a ***minor*** effect on patient's general QOL.

- mild awareness of symptoms in patients with persistent/permanent AF, or
- rare episodes (e.g. less than a few per year) in patients with paroxysmal or intermittent AF

Class 3

Symptoms attributable to AF have a ***moderate*** effect on patient's general QOL.

- moderate awareness of symptoms on most days in patients with persistent/permanent AF, or
- more common episodes (e.g. more than every few months) or more severe symptoms, or both, in patients with paroxysmal or intermittent AF

Class 4

Symptoms attributable to AF have a ***severe*** effect on patient's general QOL.

- very unpleasant symptoms in patients with persistent/paroxysmal AF and/or
- frequent and highly symptomatic episodes in patients with paroxysmal or intermittent AF and/or
- syncope thought to be due to AF and/or
- congestive heart failure secondary to AF

Appendix I. Six minute hall walk test instructions

The 6-minute hall walk test (6 MHW) is a functional performance exercise that must be completed at baseline, and at follow-up visits. Although the test is simple and safe, it requires careful standardization so that each participant, across all study centres, performs the test in an identical manner. Studies have shown that variations in the 6 MHW test environment and in instructions may influence walking distance scored, causing the test to become less precise and the data less valid.

The test will be conducted in an enclosed corridor that is:

- Free of traffic, obstacles and distractions
- A pre-measured 30.5 meters (100 feet) long length of corridor should be used for the test. Chairs should be placed at each end of the hallway.
- The hallway should be marked for ease of measurement. This will help to record the exact distance walked when the command to stop walking has been given.

Preparation:

- Ensure you have a stopwatch and a measuring tape
- Patients may eat a light meal 3 to 4 hours prior to the walk test

Instruct the participant of the following:

- That the purpose of the test is to find out how far they can walk in six minutes
- That they should walk from end to end as many times as they can in six-minutes
- That the most important part of the test is that you cover as much distance as possible in the 6 minutes
- That they can stop to rest if they need to, but they should remain in the same spot and resume when they are ready
- They need to stop walking and remain where they are when you announce the end of six minutes

During the test:

- The test administrator will need to record each pass from chair to chair during the 6 minutes
- Reassure the patient every 30 seconds by saying one of two phrases **"You're doing well"** or **"Keep up the good work"** facing the walker while speaking. You should be very careful that an **even and moderate level** of enthusiasm is maintained in your voice.
- Do not make small talk or converse with the walker during the 6 MHW.
- If the patient slows down and expresses that he or she wants to rest the following information should be delivered "If you need to you can stop and rest, just remain in your spot until you are ready to start again". **DO NOT** stop the clock until 6 minutes has elapsed.
- The walk test administrator should call out the time at 2 minute intervals using the following phrases: **"You have walked 2 minutes"**, **"You have walked 4 minutes"**
- When the 6 minutes have elapsed, the person administering the walk test should say "Stop, remain where you are for just a minute.

Post 6 MHW Test:

- The test administrator will need to count the lengths (distance one way) walked during the test time and the length of the partial lap completed

Data to be collected:

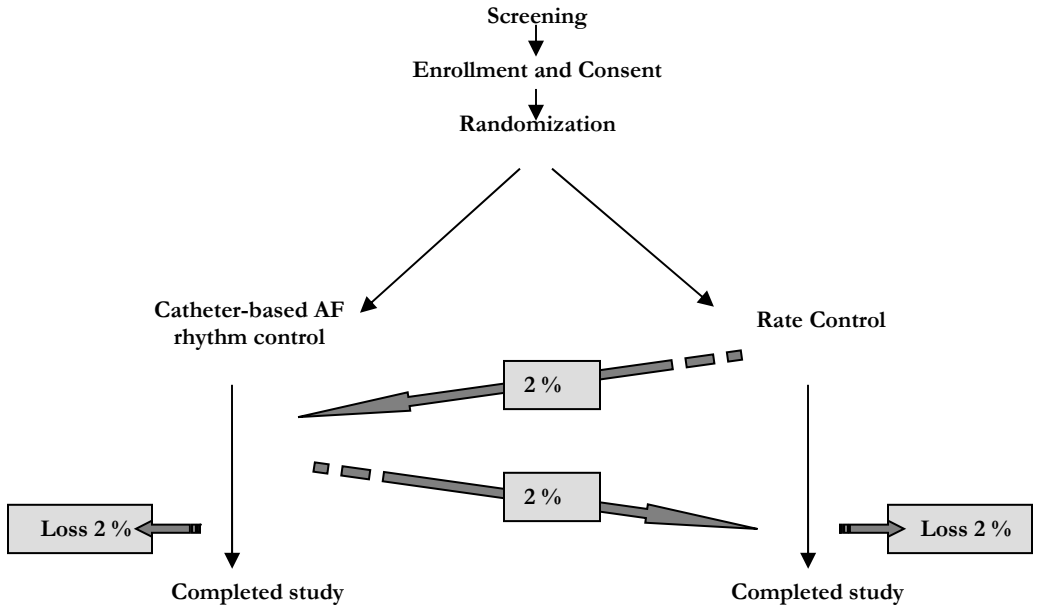
- patient study number, date of the test, total distance walked on the case report form and whether or not the patient is symptomatic.

Appendix J. Sample Size Calculation

Primary Outcome
Composite Event Rate (Power=80%, alpha=0.05) Two-sided log rank test H0: S1=S2

Comp Rate	RRR	S1 prop survive	S2 prop Survive	Survive period	Accrual	F/U	S1 Loss to F/U	S2 Loss to F/U	S1 Cross over	S2 Cross over	IF	Total N
17%	30%	0.83	0.881	1 year	3 yr	2 yr	2%	2%	2%	2%	1.02	600

Notes:
PASS 2000 ® was used to calculate the sample size N_0 without the crossover and IF adjustment.
The Crossover adjustment is $\frac{1}{(1-R_1-R_2)^2} \times N_0$ where R_1, R_2 are the crossover rates.[1] IF: An O'Brien Fleming alpha spending function inflation factor (IF) of 1.02 was used to adjust the sample size for interim analysis.



Summary Statements: A two sided log rank rest with an overall sample size of 600 patients (300 in each group) will achieve 80% power at a 0.05 significance level to detect a difference of 0.051 between 0.83 (group 1) and 0. 881 (group 2). These are the proportions without primary endpoint in groups 1(control) and 2 (experimental). Patients entered the study during an accrual period of 3 years. 50% enrollment was completed when 50% of the accrual time had passed.

[1] Friedman, L.M., Furberg, C.D. and DeMets, D.L., (1996) *Fundamentals of Clinical Trials*. Boston: John Wright PSG Inc.

Appendix K. Economical analysis details

ECONOMIC EVALUATION

Analysis will be conducted in two forms. First, a short term cost utility analysis will be conducted with costs and quality adjusted life years (QALYs) assessed within a time period of two years from entry into the clinical trial: the minimum follow up period within the clinical trial. Secondly, a long term cost utility analysis whereby long-term outcomes will be assessed through extrapolation of data from the clinical trial using a Markov model. In both analyses, the cost effectiveness of catheter ablation-based AF rhythm control as compared with rate control will be assessed in terms of incremental cost per quality adjusted life year (QALY) gained. All analyses will conform to Canadian guidelines for economic evaluation (CADTH 2006).

Short Term Cost Effectiveness Analysis

Time Horizon

Analysis will be conducted for the minimum duration of follow up within the clinical trial (two years).

Perspective

Analysis will be conducted from the health care system perspective.

Comparators

The comparators adopted will be the same as within the RCT: catheter ablation-based AF rhythm control versus rate control.

Resource Use

Resource use will be measured through questionnaires completed during the initial hospitalization for those receiving catheter and ablation and subsequent hospitalizations and during follow up. A unit cost will be applied to each type of resource. Total cost is estimated as the weighted sum of resource use (the sum of the product of the number of each resource item and its unit cost).

Resource Item	Measurement	Source of Cost
Hospitalization	Number of bed days by type of ward and principal diagnosis	Ontario Case Costing Initiative
Medication – in hospital	Drug, dosage and number	Hospital pharmacies
Medication – outpatient	Drug, dosage and number	Provincial drug formulary (Ministry of Health and Long Term Care 2010)
Physician consultation	Number by type of physician	Provincial fee schedule (Ministry of Health and Long Term Care 2008)
Diagnostic tests	Number by type of test	Provincial fee schedule (Ministry of Health and Long Term Care 2008)
Surgical procedures • Including catheter ablation	Number by type of procedure	Ontario Case Costing Initiative Provincial fee schedule (Ministry of Health and Long Term Care 2008)
Medical devices • Including pacemakers	Number by type of device	Manufacturers and hospital finance departments

The resources covered, method of measurement and the data source for their unit costs are listed below:

Quality Adjusted Life Years (QALYs)

QALYs will be measured for each patient within the clinical trial. Utility values will be estimated for each patient using the EQ5D instrument (Rabin et al. 2001). The EQ5D is a five dimension quality of life instrument designed to elicit utility values for patient's current health status. It will be completed at baseline, 2 months4 months 6 months and every six months afterwards. QALYs will be assessed using area under the curve methodology using the utility values elicited from patients.

Primary Analysis

The cost per QALY gained will be obtained through the difference in average costs of the two interventions divided by the difference in average QALYs.

Analysis of uncertainty

The uncertainty concerning the incremental cost, the incremental QALYs and the incremental cost-effectiveness ratio will be estimated by conducting probabilistic analysis through non parametric bootstrapping (Chaudhary and Stearns 1996). Bootstrapping allows estimation of the dispersion around an outcome of interest. With bootstrapping, the study sample is treated as the patient population. We then re-estimate the study sample through drawing repeated random samples of the same size as the original sample. This is done by drawing individual patient samples with replacement from the original data.

For this study, we will obtain 5000 estimates of costs and QALYs for each strategy. This approach will be used to derive 95% certainty intervals around the difference in costs, outcomes and, where pertinent, the incremental cost per outcome. These certainty intervals will be estimated using the bias corrected percentile method (Campbell and Torgerson 1999).

Results from the bootstrapping exercise will also be used to depict cost effectiveness acceptability curves (CEACs). CEACs are a graphical representation of the probability that a treatment may be cost effective given alternate dollar values placed on an outcome (van Hout et al. 1994). This will allow estimation of the probability that the experimental treatment can be considered cost effective given the available data.

Long Term Cost Utility Analysis

Analysis

Analysis will take the form of a cost utility analysis with the cost effectiveness assessed in terms of incremental cost per quality adjusted life year (QALY) gained. Analysis will be conducted through derivation and population of a Markov model (Briggs and Sculpher 1998). Base case analysis will be conducted for a patient cohort with the mean age of those within the whole patient population.

Comparators

The comparators adopted will be the same as within the RCT: catheter ablation-based AF rhythm control versus rate control.

Time Horizon

The time horizon will be 40 years with a 5% discount rate and a cycle length of one year.

Perspective

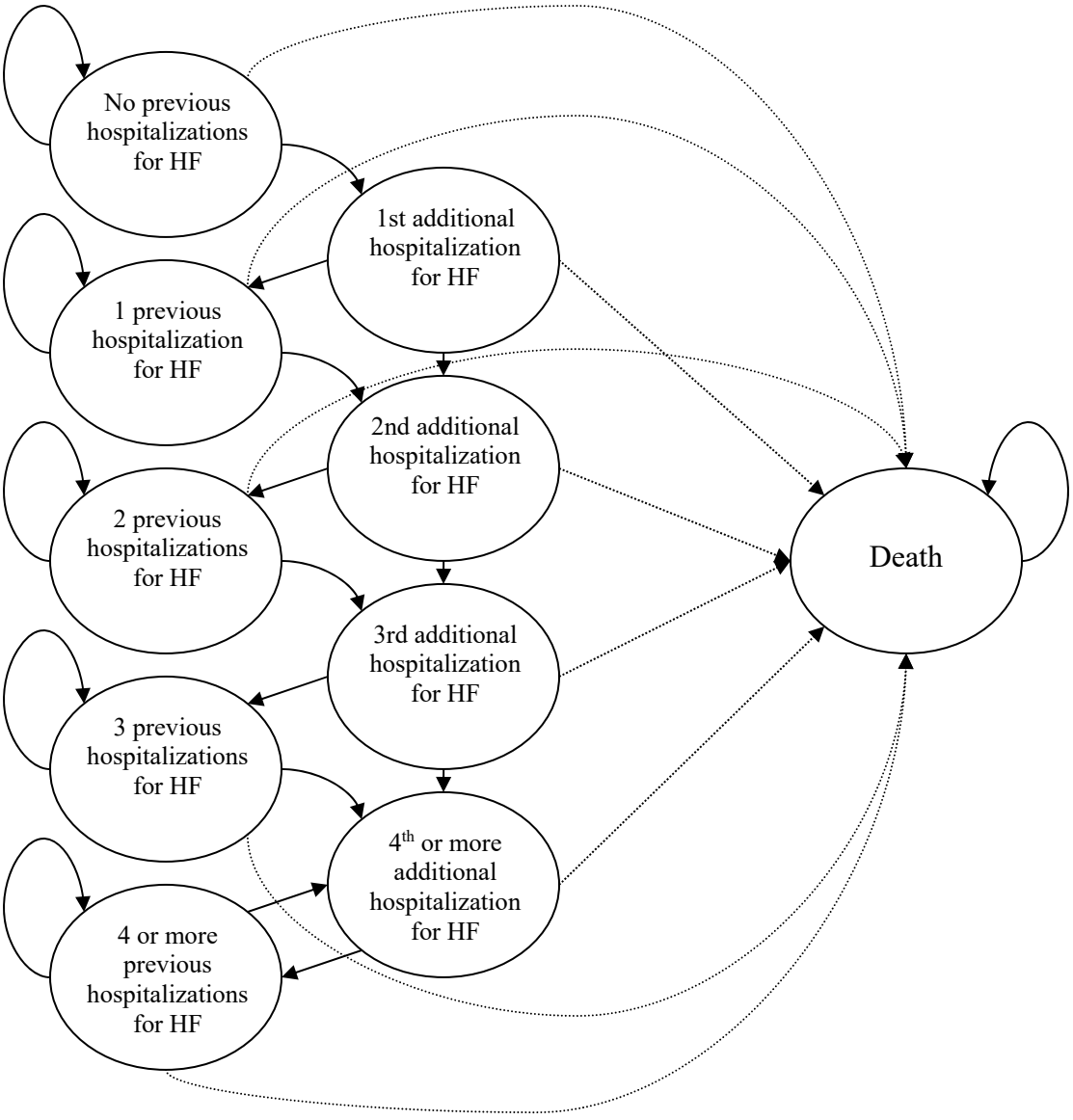
Analysis will be conducted from the health care system perspective.

Markov Model

A Markov model depicts the progression of a patient cohort over time through different health states relating to their initial health condition. The model will necessarily simplify the progression of disease. Progression of disease severity is modeled based on the number of

previous hospitalizations for HF experienced by the patient cohort (Figure 1). This is similar to other disease models adopted for economic analysis of heart failure interventions (Delea et al. 1999, Georgiou et al. 2001, Morimotoa et al. 2004 Paul et al. 1994). The underlying assumption of the model is as the severity of disease increases the probability of further hospitalization and the probability of death will increase. Thus, the greater the number of previous hospitalizations, the greater the probability of further hospitalizations and mortality.

Figure 1: Schematic of Markov Model



The Markov model will estimate the proportion of a patient cohort which will be in each health state at the end of each cycle (year). These proportions can be weighted by the appropriate costs and utility value for each state. These can then be summed and discounted and added to short term costs and utilities to estimate the discounted cost and QALYs for each treatment option.

Probability Estimates

Based on the design of the model, the following probabilities will be required:

- Annual probability of mortality
    - Specific to number of previous HF related hospitalizations
- Annual probability of rehospitalizations
    - Specific to number of previous HF related hospitalizations
- Probability of mortality during hospitalization
    - Specific to number of previous HF related hospitalizations

For the period covered by the clinical trial, probabilities will be obtained directly from the clinical trial. The probabilities of mortality and hospitalization will be estimated using Weibull models relating to time to event and will be treatment specific. The probabilities beyond the trial duration will be obtained through a thorough literature review and will be independent of initial treatment. Thus, treatment will only impact progression beyond the trial duration through the proportion of patients in each health state at the end of the trial period.

The probability of noncardiovascular death will be obtained from the most recent Statistics Canada life tables (Statistics Canada 2006).

Costs

For the events during the initial two-year period, costing will be conducted as detailed for the short term cost effectiveness analysis. For the period post the trial, the costs for HF hospitalization and the expected cost of HF management outside of hospitalizations will be obtained directly from the clinical trial. Costs will not be assumed to vary by treatment regimen – only the probability of resource related events – i.e. hospitalizations.

Utilities

Utility values are required for the health states within the model: i.e. values specific to the number of previous hospitalizations as a proxy for disease severity. A utility value for patients based on their previous number of hospitalizations will be obtained from the utility data collected within the clinical trial. For the period of the trial duration, this will be estimated for each treatment regimen. Post the period of trial, the estimate for all patients will be used.

Primary analysis

The cost per quality adjusted life year (QALY) gained will be obtained through the difference in average costs of the two programs divided by the difference in average QALYs. Costs will be obtained from adding short term costs to the weighted sum of costs in the post trial period. QALYs will be obtained from adding short term utility values to the weighted sum of utility values in the post trial period

Analysis of uncertainty

Univariate sensitivity analysis will be conducted to assess the robustness of the study's results to changing assumptions within the model

In addition, Monte Carlo simulation (MCS) will be conducted to provides estimates of the uncertainty surrounding the incremental cost-effectiveness ratio (Briggs 2000). MCS involves obtaining several estimates of outcomes by re-running the model employing different values for each data input randomly selected from that variable's probability distribution. For this analysis, the MCS will involve obtaining 5000 estimates of the incremental costs and QALYs associated with each imaging modality. The degree of uncertainty around the estimates will be expressed in terms of 95% confidence intervals around these estimates, as well as a cost effectiveness

acceptability curve which presents the probability that each procedure is optimal given different willingness to pay for an additional QALY.

Analysis of Variability

Variability will be assessed through stratified analysis incorporating a variety of relevant factors: e.g. age, number of HF related hospitalizations prior to entry into the trial and LV function (Coyle et al. 2004)

Value of Information Analysis

A value of information analysis will be performed in order to identify which parameters contribute most to the uncertainty of the study results within the long term cost effectiveness study.

Methods

Methods for estimation of the expected value of perfect partial information are as follows (Coyle and Oakley2008):

1. *Notation*

Standard notation relating to treatment options, costs, effects, cost effectiveness and parameters.

- T is the set of alternative treatment options with an individual treatment option represented by t_j. Thus, we wish to determine which treatment option is optimal.
- E_{t_1} is defined as the expected value of health benefits (e.g. QALYs) from treatment t_1
- C_{t_1} is the expected value of costs.

The net monetary benefit (NMB) for t_1 is defined as:

$$NB_{t_1} = \lambda * E_{t_1} - C_{t_1}$$

where

$$\lambda = a\ decision\ maker's\ maximum\ willingness\ to\ pay\ for\ a\ unit\ of\ health\ benefit$$

The incremental net benefit (INB) when comparing two treatment options (t_1 and $t_{2)}$ is defined as:

$$INB_{t_1 t_2} = \lambda * \left(E_{t_1} - E_{t_2}\right) - \left(C_{t_1} - C_{t_2}\right)$$

The treatment with the greatest net benefit (NB) can be considered the optimal treatment (t*).

- X will represent the set of k data parameters (X_1,….,X_k) used to estimate the cost and effects of the alternative treatment options.
- X_p is a sub group of parameters within X, whilst X_i represents an individual parameter.
- X_i^c and X_p^c denote the complement sets of input parameters: i.e. all members of X other than X_i or X_p.

2. *Methods*

The expected value of perfect partial information (EVPPI) for an individual parameter X_i is defined as:

$$\mathrm{EVPPI}_{X_i} = \mathrm{E}_{X_i}\left[\max_t \mathrm{E}_{X|X_i}\left(\mathrm{NB}_t \mid X_i\right)\right] - \mathrm{NB}_{t^*}$$

EVPPI for a sub-group of parameters X_p is defined as:

$$EVPPI_{X_p} = E_{X_p}\left[\max_t E_{X|X_p}\left(NB_t \mid X_p\right)\right] - NB_{t*}$$

If INB is multi-linear)or almost multi linear) in X_i^c (or X_p^c) (i.e. all parameters within the complement set have a linear relationship with INB), EVPPI for X_i (or X_p) can be estimated as follows:

One random value $X_p^{(j)}$ will be generated from the joint distribution of X_p. The net benefit for each treatment option t will be calculated using parameter values $X_p = X_p^{(j)}$and $X_p^c = E(X_p^c | X_p = X_p^{(j)})$. This will give the value of $E(NB_t | X_p = X_p^{(j)})$. The maximum of the net benefits will be obtained using $\max_t E(NB_t | X_p = X_p^{(j)})$

These steps will be repeated J times. EVPPI will be estimated by
$\Sigma_{j=1}^{J} \max_t E(NB_t | X_p = X_p^{(j)}) / J - NB_{t*}$
(Coyle)

3. *Results*

The EVPPI for all parameters within the model will be estimated. The results of this analysis will show which parameter contribute the most to the underlying uncertainty within the economic analysis and thus, where there is the greatest need for future research.

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Appendix L. Participating Centres

A list of the Centres that will participate in RAFT-AF trial

Canada:
QE II Health Science Centre, Halifax, Nova Scotia
Institut Universitaire de Cardiologie et de Pneumologie de Quebec, Ste. Foye, Quebec
CHUS Centre Hospitalier Universitaire de Sherbrooke, Quebec
Montreal Heart Institute, Montreal, Quebec
McGill University Health Centre, Montreal, Quebec
Hopital de Sacre Couer de Montreal, Montreal, Quebec
CHUM Hopital Notre Dame, Montreal, Quebec
U. of Ottawa Heart Institute, Ottawa, Ontario
Kingston General Hospital, Kingston, Ontario
Southlake Regional Health Centre, Newmarket, Ontario
Sunnybrook Health Sciences Centre, Toronto, Ontario
Toronto General Hospital, University Health Network, Toronto, Ontario
Hamilton Health Science Centre, Hamilton, Ontario
London Health Science Centre, London, Ontario
Mazankowski Alberta Heart Institute, Edmonton, Alberta
Libin Cardiovascular Institute of Alberta, Calgary, Alberta
Vancouver General/St. Paul's Hospital, Vancouver, BC
Royal Jubilee Hospital, Victoria, BC
Royal Columbian Hospital, New Westminster, BC

Potential Participating sites outside of Canada:
St. Charles Gairdner Hospital, Perth, Australia
Centro Medico Imbanaco, Cali, Colombia
Heart Institute of Sao Paulo Medical School, San Paulo, Brazil
Universidade Federal de Sao Paul, Sao Paulo, Brazil
Instituto de Cardiologia, Fundecao Universitaria de Cardiologia, Porto Alegre, Brazil
University Hospital, Geneva, Switzerland
CHU de Rouen Rouen Cedex France
Hôpital Haut Leveque Bordeaux, France
CHU Daig Nancy Nancy, France
Marseille CH St Joseph Marseilles Toulouse, France
François Rabelais University and Hospital Trousseau Tours, France
Ancien interne des Hôpitaux, France
Kärnsjukhuset, Skövde Hospital Skövde, Sweden
Karolinska University Stockholm, Sweden
Seoul National University Hospital, Korea
Korea University Medical Center, Korea
Yonsei University Health System, Korea
Opsedale regionale di Treviso Treviso, Italy

Appendix M. RAFT article by Tang et al, 2009

Included with submission: Tang, A.S., et al, *Resynchronization/defibrillation for ambulatory heart failure trial: rationale and trial design.* Curr Opin Cardiol, 2009.

Appendix N. Hicks, Karen A.et al, 2017 Cardiovascular and Stroke Endpoint Definitions for Clinical Trials (J Am Coll Cardiol 2018;71:1021–34) Appendix 9

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THE PRESENT AND FUTURE

STATE-OF-THE-ART REVIEW

2017 Cardiovascular and Stroke Endpoint Definitions for Clinical Trials

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Extracted from Article:

Appendix 9. Definition of Heart Failure Event

A Heart Failure Event includes hospitalization for heart failure and may include urgent outpatient visits. HF hospitalizations should remain delineated from urgent visits. If urgent visits are included in the HF event endpoint, the number of urgent visits needs to be explicitly presented separately from the hospitalizations.

A Heart Failure Hospitalization is defined as an event that meets **ALL** of the following criteria:

1) The patient is admitted to the hospital with a ***primary diagnosis*** of HF
2) The patient's length-of-stay in hospital extends for **at least 24 hours** (or a change in calendar date if the hospital admission and discharge times are unavailable)
3) The patient exhibits documented new or worsening symptoms due to HF on presentation, including **at least ONE** of the following:
    a. Dyspnea (dyspnea with exertion, dyspnea at rest, orthopnea, paroxysmal

nocturnal dyspnea)
   b. Decreased exercise tolerance
   c. Fatigue
   d. Other symptoms of worsened end-organ perfusion or volume overload (must be specified and described by the protocol)

4) The patient has objective evidence of new or worsening HF, consisting of **at least TWO** physical examination findings **OR** one physical examination finding and **at least ONE** laboratory criterion), including:
   a. Physical examination findings considered to be due to heart failure, including new or worsened:
      i. Peripheral edema
      ii. Increasing abdominal distention or ascites (in the absence of primary hepatic disease)
      iii. Pulmonary rales/crackles/crepitations
      iv. Increased jugular venous pressure and/or hepatojugular reflux
      v. S_3 gallop
      vi. Clinically significant or rapid weight gain thought to be related to fluid retention
   b. Laboratory evidence of new or worsening HF, if obtained within 24 hours of presentation, including:
      i. Increased B-type natriuretic peptide (BNP) / N-terminal pro-BNP (NT-proBNP) concentrations consistent with decompensation of heart failure (such as BNP > 500 pg/mL or NT-proBNP > 2,000 pg/mL). In patients with chronically elevated natriuretic peptides, a significant increase should be noted above baseline.
      ii. Radiological evidence of pulmonary congestion
      iii. Non-invasive diagnostic evidence of clinically significant elevated left- or right-sided ventricular filling pressure or low cardiac output. For example, echocardiographic criteria could include: septal or lateral E/e' > 15 or > 12, respectively; D-dominant pulmonary venous inflow pattern; plethoric inferior vena cava with minimal collapse on inspiration; or decreased left ventricular outflow tract (LVOT) minute stroke distance (time velocity integral [TVI])

      OR

      iv. Invasive diagnostic evidence with right heart catheterization showing a pulmonary capillary wedge pressure (pulmonary artery occlusion pressure) ≥ 18 mmHg, central venous pressure ≥ 12 mmHg, or a cardiac index < 2.2 L/min/m^2

   Note: All results from diagnostic tests should be reported, if available, even if they do not meet the above criteria, because they provide important information for the adjudication of these events.

5) The patient receives **at least ONE** of the following treatments specifically for HF:
   a. Significant augmentation in oral diuretic therapy (e.g., doubling of loop diuretic dose, initiation of maintenance loop diuretic therapy, initiation of combination diuretic therapy)
   b. Initiation of intravenous diuretic (even a single dose) or vasoactive agent

(e.g., inotrope, vasopressor, vasodilator)

c. Mechanical or surgical intervention, including:
    i. Mechanical circulatory support (e.g., intra-aortic balloon pump, ventricular assist device, extracorporeal membrane oxygenation, total artificial heart)
    ii. Mechanical fluid removal (e.g., ultrafiltration, hemofiltration, dialysis)

General Considerations (HF Hospitalization)

Combination diuretic therapy could include 1) a thiazide-type diuretic (e.g., hydrochlorothiazide, metolazone, chlorothiazide) plus a loop diuretic; or 2) mineralocorticoid receptor antagonist (MRA) (e.g., spironolactone or eplerenone) plus a loop diuretic.

An **Urgent Heart Failure Visit** is defined as an event that meets all of the following:

1) The patient has an urgent, unscheduled office/practice or emergency department visit for a primary diagnosis of HF, but not meeting the criteria for a HF hospitalization
2) The patient meets all signs and symptoms for HF hospitalization [i.e., 3) symptoms, 4) physical examination findings/laboratory evidence of new or worsening HF, as indicated above]
3) The patient receives **at least ONE** of the following treatments specifically for HF:
    a. Initiation of intravenous diuretic or vasoactive agent (e.g., inotrope, vasopressor, or vasodilator)*
    b. Mechanical or surgical intervention, including:
        i. Mechanical circulatory support (e.g., intra-aortic balloon pump, ventricular assist device, extracorporeal membrane oxygenation, total artificial heart)
        ii. Mechanical fluid removal (e.g., ultrafiltration, hemofiltration, dialysis)

***Note that significant augmentation of oral diuretic therapy will NOT be sufficient to fulfill the urgent HF visit criteria.**

General Considerations (Urgent HF Visit)

1. Clinic visits for ***scheduled*** administration of HF therapies or procedures (e.g., intravenous diuretics, intravenous vasoactive agents, or mechanical fluid removal) **do NOT** qualify as non-hospitalized HF events.

Appendix O. Treatment for Heart Failure: Endpoints for Drug Development Guidance for Industry. June 2019. US Department of Health and Human Services FDS, Center for Drug Evaluation and Research (CDER). Center for Biologics Evaluation and Research (CBER) Clinical

Treatment for Heart Failure: Endpoints for Drug Development

Guidance for Industry

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within ___ days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit electronic comments to https://www.regulations.gov. Submit written comments to the Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document, contact Norman Stockbridge at 301-796-2240 or (CBER) Office of Communication, Outreach, and Development at 240-402-8010.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

June 2019
Clinical

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Treatment for Heart Failure: Endpoints for Drug Development Guidance for Industry[1]

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the FDA staff responsible for this guidance as listed on the title page.

I. INTRODUCTION

This guidance has two purposes: 1) to make it clear that an effect on symptoms or physical function, without a favorable effect on survival or risk of hospitalization, can be a basis for approving drugs[2] to treat heart failure; and 2) to provide recommendations to sponsors on the need to assess mortality effects of drugs under development to treat heart failure.[3]

This guidance reflects the Food and Drug Administration's (FDA's) current thinking about developing drugs to treat heart failure. Areas of uncertainty (highlighted in boxes in this guidance) remain, and FDA welcomes discussion and alternative approaches.

This guidance pertains primarily to treating chronic heart failure. Development of drugs to treat acute heart failure and pediatric considerations are discussed briefly. This guidance applies to both heart failure with reduced ejection fraction (HFrEF) and heart failure with preserved ejection fraction (HFpEF).

In general, FDA's guidance documents do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

[1] This guidance has been prepared by the Division of Cardiovascular and Renal Products in the Center for Drug Evaluation and Research (CDER) in cooperation with the Center for Biologics Evaluation and Research (CBER) at the Food and Drug Administration.

[2] For the purposes of this guidance, all references to *drugs* include both human drugs and biological products unless otherwise specified.

[3] For purposes of this guidance, unless otherwise specified, references to "drugs" and "drug products" include drugs submitted for approval or approved under section 505(b) or (j) of the FD&C Act and biological products licensed under section 351 of the PHS Act, other than biological products that also meet the definition of a device in section 201(h) of the FD&C Act (21 U.S.C. 321(h)).

II. BACKGROUND

Heart failure afflicts approximately 6.5 million patients in the United States and 26 million patients worldwide. As the U.S. population ages, the prevalence of heart failure is increasing, with approximately 550,000 new cases diagnosed annually.

Heart failure causes substantial mortality and morbidity and has major effects on physical function and quality of life. The annual mortality rate of patients with heart failure is approximately 10%. Hospitalization is common, with approximately 30% of heart failure patients hospitalized annually. Despite optimal management, most patients with heart failure have troublesome symptoms, including dyspnea and fatigue.

Drugs of several pharmacologic classes (angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), beta blockers, mineralocorticoid receptor antagonists (MRAs)) that have been approved in the past 2 decades significantly improve heart failure outcomes, including physical function, risk of hospitalization, and survival, in patients with reduced ejection fraction. Despite these therapies, the disease continues to shorten lives and cause significant disability and symptoms. Diuretics, both thiazides and loop diuretics, are also widely used to reduce signs and symptoms of heart failure, although their outcome effects (death and risk of hospitalization) have not been evaluated. These facts point to a need for new drugs to treat heart failure. In addition, there are no effective treatments for HFpEF, which represents approximately 50% of heart failure cases.

Unfortunately, some drugs (e.g., milrinone and flosequinan) intended to treat heart failure were found to have favorable effects on exercise capacity and symptoms but were subsequently found to increase mortality. This experience led FDA to ask sponsors to assess the mortality effects of such drugs, usually prior to approval. The intent was not to require demonstration of improved survival—although that would be an important outcome—but rather to provide reasonable assurance that the drug did not increase mortality.

Subsequently, some sponsors and other stakeholders reported a belief that favorable effects on mortality and morbidity (specifically, hospitalization for heart failure) were required to approve drugs to treat heart failure. The approvals of ACE inhibitors, ARBs, beta blockers, and sacubitril-valsartan may have contributed to this impression, as their approvals were based on these endpoints. In fact, although important, favorable effects on survival and hospitalization rates are not required for FDA approval.

A drug that improves symptoms or function when added to standard of care would be valuable even if it did not improve survival or hospitalization. Moreover, it is possible that if a drug provided substantial and persistent improvement in symptoms or function, especially for patients with New York Heart Association Class III or IV heart failure, some decrease in survival would be acceptable.

The type of evidence of effectiveness needed to support the approval of drugs to treat heart failure does not differ from the evidence needed to support the approval of drugs intended to

treat other conditions: substantial evidence demonstrating that the drug improves how a patient feels, functions (i.e., symptomatic or functional improvement), or survives.

III. MORTALITY DATA: PURPOSE AND REQUIREMENTS

Mortality data can serve two purposes in the context of developing drugs to treat heart failure:

1) As a **primary efficacy endpoint**, a decrease in mortality provides evidence of effectiveness in heart failure trials.

2) As a **safety endpoint**, mortality data provides an assessment of the possibility of an adverse effect on survival.

When approval is based on improvement of symptoms or function, FDA will consider the following factors in determining whether and when (i.e., pre- or postapproval) additional mortality data are needed:

- **The mortality and other safety findings of pharmacologically similar drugs**. For example, the safety profiles of ACE inhibitors, ARBs, beta blockers, MRAs, and digoxin are well-established. The safety of a new drug in these classes could be supported by existing data, and additional information on mortality might not be needed. In general, drugs with novel mechanisms of action are more likely to require mortality data.

- **Planned duration of exposure**. If the planned treatment is for short-term use (typically less than 10 days), for example, treatment of acute exacerbations, there is generally no requirement for long-term mortality data.

- **The mortality and other safety findings of the drug in a closely related population in which at least a subset of the patients had heart failure or were at risk of heart failure**. For example, many patients with coronary artery disease or long-standing diabetes have or will develop heart failure. Results of studies in such populations could therefore support the safety of the drug in a heart failure population.

- FDA believes there should be further discussion about whether the nature, magnitude, and clinical importance of a symptomatic benefit, considered with the demonstrated risks, could justify deferral or omission of outcome studies to assess mortality.

- When mortality data are needed, FDA believes it would be useful to discuss the risk of mortality that should be ruled out in outcome studies and whether the acceptable upper bound should be influenced by the drug's demonstrated benefits and risks.

- FDA believes there should be discussion about whether and when an increased risk in mortality could be acceptable for a drug with an important symptomatic benefit.

When a mortality study is needed, sponsors should consider simple outcome studies (i.e., with selective data collection, which are highly feasible in patients with heart failure, particularly those with advanced disease, because the mortality rate is high in such patients).

IV. EFFICACY ENDPOINTS RELATED TO HOW PATIENTS FEEL AND FUNCTION

Evidence of effectiveness for a heart failure drug could be based on improvements in symptoms (e.g., dyspnea, fatigue, edema) and/or function (e.g., walking, exercising, performing other activities of daily living).

Endpoints acceptable to FDA include individual symptoms or a composite symptom score, exercise capacity, functional capacity, New York Heart Association functional class, and measures of activity/daily living. FDA will consider trials that use novel endpoints, including other clinical outcome assessments, other measures of functional capacity, and measures of daily activity (e.g., accelerometry data). For endpoints that can be influenced by expectation bias or motivation (e.g., 6-minute Walk Test), blinding of investigators and subjects is critically important.

Sponsors should consult with the Agency early in the drug-development process to obtain agreement on proposed endpoints.

For guidance on patient-reported outcome measures, see the guidance for industry *Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims* (December 2009).

V. HOSPITALIZATION AND OUTPATIENT INTERVENTION

Hospitalization represents an important clinical outcome, reflecting worsening function and/or symptoms, interruption of daily activities, and superimposed risks and inconveniences.

Hospitalization has been widely used as a measure of "morbidity" in trials of drugs for heart failure, either as an independent endpoint or as a component of a composite endpoint that includes mortality. Typically, these endpoints have been assessed as time-to-first events.

Acceptable approaches to quantifying hospitalization (and outpatient interventions) for use as an endpoint include binary endpoints (hospitalization (yes/no)), number of hospitalizations, time-to-initial hospitalization, time alive (or at home) and out of the hospital, and time to recurrent hospitalizations.

The Agency encourages discussion of the pros and cons of capturing all-cause hospitalization versus cause-specific hospitalization.

As heart failure treatment moves away from the inpatient setting, FDA will consider alternative endpoints that reflect clinically important worsening symptoms leading to an intervention (e.g., treatment in an emergency department, a same-day access clinic, or an infusion center) or unscheduled visits to a healthcare provider for administration of an intravenous diuretic.

VI. BIOMARKERS AND SURROGATE ENDPOINTS

To date, no biomarkers have been validated as surrogate endpoints for clinical benefit in heart failure. For patients with symptomatic heart failure, it is generally possible to assess directly how individuals feel, function, and survive; therefore, biomarkers have little utility for evaluating drug efficacy in this setting. Biomarkers, however, can be used to characterize risk in patients with heart failure (e.g., NT pro-BNP, left ventricular ejection fraction), and such measures can be useful for prognostic enrichment. Moreover, biomarkers have utility for early proof-of-concept studies and, in particular, studies that serve as the basis for dose selection.

Where heart failure is a consequence of long-term myocardial damage (e.g., infiltrative cardiomyopathies), disease advancement can be slow, and there is great interest in therapies that may slow or prevent disease progression. For such diseases, manifestations of a clinical benefit can take years to observe, and intermediate clinical endpoints and surrogate endpoints[4] could support accelerated approval. For example, consider a therapy that leads to a reduction, reversal, or prevention of myocardial infiltration. A biomarker that assesses myocardial damage or infiltration, which is not a direct measure of clinical benefit, could be considered a reasonably likely surrogate endpoint[5] to serve as the basis for accelerated approval if certain conditions are

[4] See FDA-NIH BEST (Biomarkers, EndpointS, and other Tools) Resource for the definition of intermediate clinical endpoint and surrogate endpoint: https://www.ncbi.nlm.nih.gov/books/NBK453485/.

[5] See FDA-NIH BEST (Biomarkers, EndpointS, and other Tools) Resource for the definition of reasonably likely surrogate endpoint: https://www.ncbi.nlm.nih.gov/books/NBK453485/.

199 met (see the guidance for industry *Expedited Programs for Serious Conditions – Drugs and*
200 *Biologics* (September 2017)), with subsequent verification of clinical benefit.
201
202
203 **VII. ACUTE HEART FAILURE**
204
205 Drugs developed with the intended indication of acute heart failure are generally targeted at
206 acute exacerbations of chronic heart failure. The duration of treatment is generally expected to
207 be less than 10 days.
208
209 Such drugs could be approved based on symptom relief (e.g., dyspnea, time to hospital
210 discharge, or avoidance of invasive therapies (left ventricular assist devices, dialysis)).
211
212 Safety must be assessed following drug administration (i.e., ascertainment of death and
213 rehospitalization, generally through 30 days) for drugs with a short duration of exposure.
214
215
216 **VIII. HEART FAILURE WITH PRESERVED EJECTION FRACTION**
217
218 Although HFpEF and HFrEF are pathophysiologically distinct, the same considerations apply for
219 both.
220
221
222 **IX. HEART FAILURE IN THE PEDIATRIC POPULATION**
223
224 Although a detailed discussion of heart failure in the pediatric population is out of scope of this
225 guidance, many of the principles enumerated above apply to pediatric populations.
226 Demonstration of clinical benefit may not be needed in pediatric patients with heart failure when
227 the disease in pediatric patients is similar to that in adults and the drug is expected to exert the
228 same effect irrespective of the underlying pathophysiology of heart failure (e.g., diuretics).
229 There may, however, be unique safety considerations when developing drugs to treat heart
230 failure in a pediatric population (e.g., effects on growth and development and hormonal
231 changes).
232
233 Guidance documents specific to pediatric drug development should be consulted for additional
234 information. They include the following guidances for industry:
235
236 • *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study*
237 *Plans and Amended Initial Pediatric Study Plans* (March 2016)
238
239 • *E11 Clinical Investigation of Medicinal Products in the Pediatric Population* (December
240 2000)
241
242 • *E11(R1) Addendum Clinical Investigation of Medicinal Products in the Pediatric*
243 *Population* (April 2018)

- *General Clinical Pharmacology Considerations for Pediatric Studies for Drugs and Biological Products* (December 2014)

- *Nonclinical Safety Evaluation of Pediatric Drug Products* (February 2006)