McMaster University
DigitalCommons@McMaster

Open Access Dissertations and Theses | Open Dissertations and Theses

10-1-2011

REVISED STRATEGY OF SYNCOPE DIAGNOSIS IN THE EMERGENCY ROOM AT THE GENERAL HOSPITAL (RESASTER): A CLUSTER RANDOMIZED TRIAL

Juan C. Guzman
McMaster University, guzmanjc@mcmaster.ca

Follow this and additional works at: http://digitalcommons.mcmaster.ca/opendissertations

Part of the Cardiology Commons, Diagnosis Commons, and the Emergency Medicine Commons

Recommended Citation
Guzman, Juan C., "REVISED STRATEGY OF SYNCOPE DIAGNOSIS IN THE EMERGENCY ROOM AT THE GENERAL HOSPITAL (RESASTER): A CLUSTER RANDOMIZED TRIAL" (2011). *Open Access Dissertations and Theses.* Paper 6414.

This Thesis is brought to you for free and open access by the Open Dissertations and Theses at DigitalCommons@McMaster. It has been accepted for inclusion in Open Access Dissertations and Theses by an authorized administrator of DigitalCommons@McMaster. For more information, please contact scom@mcmaster.ca.

REVISED STRATEGY OF SYNCOPE DIAGNOSIS IN THE EMERGENCY ROOM

REVISED STRATEGY OF SYNCOPE DIAGNOSIS IN THE EMERGENCY ROOM AT THE GENERAL HOSPITAL (RESASTER): A CLUSTER RANDOMIZED TRIAL

A DESIGN THESIS

By

JUAN C. GUZMAN, MD

A Thesis

Submitted to the School of Graduate Studies

In Partial Fulfilment of the Requirements

For the Degree

Master of Sciences

McMaster University

© Copyright by Juan C. Guzman, October 2011

MASTER OF SCIENCES (2011)
(Health Research Methodology)

McMaster University
Hamilton, ON

TITLE: Revised Strategy of Syncope Diagnosis In The Emergency Room At The General Hospital (RESASTER): A Cluster Randomized Control Trial

AUTHOR: Dr. Juan C. Guzman

SUPERVISOR: Dr. Lehana Thabane

NUMBER OF PAGES: xii, 121

Abstract

Background

Syncope, defined as a transient loss of consciousness (TLOC) followed by spontaneous recovery, is estimated to account for 1% to 3% of emergency department (ED) annual visits in North America. Although most potential causes of syncope are benign and self-limited, others are associated with serious morbidity and substantial mortality. Recent efforts have focused on prospective identification of ED patients with syncope who are at high risk for early serious adverse outcomes in an attempt to hospitalize them at their first visit to the ED.

Objective

The purpose of this thesis is to describe the methodological issues related to the design of a study to determine whether the Revised Strategy of Syncope Diagnosis in the Emergency Room at the General Hospital Structured Care Pathway (RESASTER-SCP) is superior to usual care in identifying patients at low risk for serious adverse outcomes presenting to the ED who can be safely discharged home.

Design and Methods

A cluster randomized trial will be conducted with EDs (16 teaching and 46 non-teaching general hospitals) as the unit of randomization and patients presenting with syncope (TLOC) as the unit of analysis. Cluster inclusion criteria include: ED located across the province of Ontario in Canada, accessibility to emergency physicians and physician specialists for the assessment of patients with syncope in the ED, hospital chief of medical staff approval of the protocol, hospital administration approval of the protocol and Hospital ethics board approval of the protocol. Cluster exclusion criteria will include hospitals with established syncope unit or specialized syncope service and pediatric hospitals. Individual participant inclusion criteria will be defined as a patient consulting for syncope in the ED, age 18 years older, with English or French language proficiency and ability to give informed consent by the patient or power of attorney. Exclusion criteria are defined as previous investigated and diagnosed cause of syncope, life expectancy less than one year according to underlying disease prognosis and

history of severe cognitive impairment or severe psychotic impairment. The primary outcome has been defined as necessary hospitalization and the secondary outcomes include: death from any cause, myocardial infarction, arrhythmia, pulmonary embolism, stroke, subarachnoid hemorrhage, significant hemorrhage, any procedural intervention to treat a related cause of syncope, any condition causing or likely to cause a return emergency visit, hospitalization for a related event within 30 days and specific syncope diagnosis. Study participants will be followed at 1, 3, 5, and 12 months after the intervention (RESASTER-SCP vs. usual care) has been applied in the ED. Intention to treat analysis will be used. The analysis will be conducted at the individual level using proportions and means according to the variable in question. Alpha level will be set at 0.05 with a power of 0.80 for the primary outcome. The study will be approved for the principal investigator institution ethics board before any recruitment of either cluster or individuals is started.

Conclusion

This thesis describes some of the methodological issues concerning the design of a cluster randomized trial aiming to determine whether the RESASTER-SCP is superior to usual care in identifying patients at low risk for serious outcomes presenting to the ED with syncope who can be safely discharged home. Thus the aim of a structured care pathway for syncope diagnosis in the ED is: (1) give the patient continuity of care, (2) reduce inappropriate hospitalizations, and (3) set standards of clinical excellence in the field.

Acknowledgments

I first wish to thank Dr. Lehana Thabane and Dr. Carlos Morillo whose mentorship, vision, guidance and enthusiasm helped foster my interest in this study field and my development as a clinician scientist. For that I will always be grateful.

I also wish to thank the other members of my thesis committee, Dr. Marek Smieja and Dr. Forough Farrokhyar to their constructive advice in the completion of this project.

I wish to acknowledge the Arrhythmia Service and Cardiology Division at the Department of Medicine of McMaster University for providing financial assistance in form of tuition stipend.

I wish to thank to my parents for their support and advice during the different steps of my academic and personal life. They sacrificed so much in order that I pursue a successful career in Medicine.

Finally, my greatest thanks to my wife Rocio, for her love, amazing support, and motivation, and for accompanied me in this long journey to become a successful physician scientist and being so patient with me during the last 13 years. I also want to dedicate this thesis to my new daughter Nicole since she has brought a lot of joy and happiness to our lives.

Table of Contents

PAGE

CHAPTER 1 INTRODUCTION AND REVIEW OF LITERATURE 1

1.1 Introduction 1

1.2 Definitions 4

1.3 Causes of syncope 6

1.3.1 Reflex syncope (Neurally mediated syncope) 9

1.3.2 Orthostatic hypotension and orthostatic intolerance syndromes 11

1.3.3 Cardiac syncope 12

1.4 Epidemiology and burden of syncope 13

1.5 Prognosis 14

1.6 Assessment of syncope in the Emergency Department 16

1.6.1 Initial evaluation 16

1.6.2 Diagnosis of syncope 17

1.6.3 Risk stratification 17

1.6.4 Evidence based risk stratification tools and clinical decision rules 20

1.6.4.1 The San Francisco Syncope Rule (SFSR) 20

1.6.4.2 OESIL (Osservatorio Epidemilogico sulla Syncope nel Lazio) risk score 22

1.6.4.3 European Society of Cardiology Guidelines on Management (Diagnosis and Management) of Syncope 23

1.6.4.4 Risk stratification of syncope in the emergency department study (ROSE) 24

1.6.4.5 Other instruments 25

1.6.5 Syncope management unit 26

1.7 Diagnosis of Syncope in the Emergency Department: A Systematic Review of Literature 28

CHAPTER 2 RESASTER STUDY DESIGN CONSIDERATIONS 34

2.1 Introduction 34

2.2 Study rationale 35

2.3 Study Hypotheses 36

2.4 Study Objectives 36

2.4.1 Primary objective 36

2.4.2 Secondary objectives 37

2.5 Selecting study design: Cluster Randomized Trial 37

2.5.1 Disadvantages and limitations of cluster randomization 40

2.5.1.1 Efficiency 40

2.5.1.2 Selection bias 40

2.5.1.3 Imbalance between study arms 41

2.5.1.4 Generalizability 42

2.6 RESASTER-SCP 42

2.7 Cluster definition and eligibility 44

2.7.1 Cluster inclusion criteria 45

2.7.2 Cluster exclusion criteria 45

2.8 Unit of inference 45

2.8.1 Patient Inclusion Criteria 46

2.8.2 Patient Exclusion Criteria 46

2.9 Participant Recruitment 46

2.10 Randomization procedures 49

2.10.1 Restricted randomization 49

2.10.2 Allocation concealment 51

2.10.3 Validity of Restricted Randomization 53

CHAPTER 3 MEASUREMENTS AND DATA COLLECTION CONSIDERATIONS 54

3.1 Introduction 54

3.2 Syncope definition in RESASTER Study 54

3.3 Primary Outcome 54

3.4 Secondary Outcomes 56

3.5 Outcomes follow-up 59

3.6 Data collection 59

CHAPTER 4 STATISTICAL CONSIDERATIONS 61

4.1 Introduction 61

4.2 Intracluster correlation coefficient 61

4.3 Sample size calculation 63

4.4 Analytical methods 68

4.4.1 Cluster-level analysis 68

4.4.2 Individual-level analysis 70

4.4.3 Proposed statistical analysis 71

4.4.3.1 Statistical tests to be conducted 71

4.4.3.2 Intention to treat analysis 73

4.4.3.3 Subgroup analysis 74

4.4.3.4 Adjustment for multiple testing 74

4.4.3.5 Study results reporting 75

CHAPTER 5 POTENTIAL DESIGN CHALLENGES AND STUDY LIMITATIONS 77

5.1 Introduction 77

5.2 Threats to Internal Validity 77

5.3 Threats to External Validity 79

5.4 Minimizing commission and omission errors 81

5.5 Pilot study 83

5.6 Issues involving losses to follow-up 86

5.7 Achieving desired power 88

5.8 Missing data handling 89

5.9 Sensitivity analysis 90

CHAPTER 6 ETHICAL AND LEGAL ISSUES 92

6.1 Source of Funding and Potential Conflicts of Interest 92

6.2 Ethical issues in cluster randomized trials 92

6.3 Health Canada Approval and trial registration 95

6.4 Risk and Benefits of the Proposed Research to Participants 96

6.5 Protection of participant's information confidentiality 97

CHAPTER 7 FUTURE DIRECTIONS AND CONCLUSIONS 98

7.1 Future Directions 98

7.2 Conclusions 99

APPENDIX A. THE SAN FRANCISCO SYNCOPE RULE (SFSR) 100

APPENDIX B. THE OESIL RISK SCORE 103

APPENDIX C. DATA COLLECTION FORMS 104

List of Figures and Tables

Page

Table 1.1.1: Conditions incorrectly diagnosed as syncope. 5

Table 1.1.2: Classification of syncope 8

Table 1.1.3: Short-term high-risk criteria, which require prompt hospitalization or intense evaluation..... 18

Table 4.1 Sample Size according to ICC and MCID 67

Table 4.2 Outcome's Method of Analysis 73

Figure 2.1 Schematic representation of RESASTER study..... 39

Chapter 1 Introduction and Review of Literature

1.1 Introduction

Syncope, defined as a transient loss of consciousness (TLOC), is estimated to account for 1% to 3% of emergency department (ED) annual visits and up to 6% of hospital admissions in North America (ACEP, 2001; Huff et al, 2007) and around the world (Ganzeboom et al, 2006; Moya et al, 2009). Although most potential causes of syncope are benign and self-limited, some are associated with significant morbidity and mortality including cardiac arrhythmias and structural heart disease (Kapoor et al, 1983).

During ED evaluation, the cause of syncope often remains unclear and management must focus on identification of the underlying condition and risk stratification in order to differentiate among patients safe for discharge and those who require emergent investigation and in-hospital management. However, methods of diagnosis vary from centre to centre and there is no uniform consensus on the best strategy to triage these patients in the ED. Recent efforts have focused on prospective identification of ED patients with syncope who are at high risk for early serious outcomes in an attempt to hospitalize them at their first visit to the ED.

Given the cost of diagnosing and treating syncope, estimated at US$2.4 billion in the United States (US) per year (Sun et al, 2005), a standardized strategy for the risk assessment of syncope in the ED and a decision rule for admission to hospital are needed to improve diagnostic yield so as to reduce morbidity and mortality associated with syncope, as well as to reduce costs for the healthcare system. Different decision rules and risk stratification scores have been proposed but they have not been systematically compared versus the conventional approach in a prospective cluster randomized trial.

The purpose of this design thesis is to present a proposal for a study, *The Revised Strategy of Syncope Diagnosis in The Emergency Room at the General Hospital: A Cluster Randomized Trial (RESASTER),* that aims to implement a simple and comprehensive structured care pathway (SCP) that will help the clinician (Emergency physicians and specialist consultants) to identify patients (presenting with syncope to the ED) at low risk of serious outcomes who can safety discharge home. RESASTER-SCP will use the previously validated San Francisco Syncope Rule (SFSR) (Quinn et al, 2004; Quinn et al, 2005; Quinn et al, 2006) and the Osservatorio Epidemiologico Sulla Sincope Nel Lazio risk score (OESIL) (Colivicchi et al, 2003) as part of a structured care pathway.

The first chapter of this thesis reviews the literature on syncope with emphasis on diagnosis and prognostic tools. The second chapter will focus on RESASTER study design including: rationale, hypotheses, primary and secondary objectives description, cluster randomized trial design considerations, the RESASTER-SCP, cluster definition and eligibility, the unit of inference participant recruitment and randomization procedures. The third chapter will focus on measurement considerations pertaining to the diagnosis of syncope as well as the selection of instruments for primary and secondary outcome measurements, outcomes follow-up and data collection. The fourth chapter will describe statistical considerations including the intracluster correlation coefficient, the sample size calculation and the planned analytical methods for the study. The fifth chapter will address potential methodological challenges that can arise during the conduction of the study including threats to internal and external validity, minimizing commission and omission errors, need of a pilot study, issues involving loss in follow-up, achieving desired power, missing data handling and sensitivity analysis. The sixth chapter will describe ethical issues pertaining to the execution of the study as well study funding. The seventh and final chapter will address clinical relevance of the results – that is, how the results of RESASTER can be applied to the clinical practice and will present a final conclusion regarding the methodological challenges that the study will face.

1.2 Definitions

According to the 2009 guidelines from the European Society of Cardiology (ESC) syncope is defined as a TLOC due to transient global cerebral hypoperfusion characterized by rapid onset, short duration, and spontaneous complete recovery (Moya et al, 2009). This recent updated definition differs from other definitions by including the cause of unconsciousness, i.e. transient global cerebral hypoperfusion. In the past, there had been some confusion both in clinical practice and in some published papers in which epilepsy, stroke or psychogenic syncope had been described as syncope. So, the guidelines clearly set out what is syncope and what is not syncope. See in Table 1.1.1 the conditions that are usually incorrectly diagnosed as syncope (Moya, 2009).

Disorders with partial or complete TLOC but without cerebral hypoperfusion
• Epilepsy • Metabolic disorders including hypoglycemia, hypoxia, hyperventilation with hypocapnia • Intoxication • Vertebrobasilar transient ischemic attack
Disorders without impairment of consciousness

• Cataplexy • Drop attacks • Falls • Functional (psychogenic or pseudosyncope) • TIA of carotid origin

Table 1.1.1: Conditions incorrectly diagnosed as syncope.

In some forms of syncope there may be a prodromal period in which various symptoms (e.g. light headedness, nausea, sweating, weakness, and visual disturbances) warn that syncope is imminent. Often, however, TLOC occurs without warning. Recovery from syncope is usually accompanied by almost immediate restoration of appropriate behaviour and orientation. Retrograde amnesia, although believed to be uncommon, it is more frequent than previously thought, particularly in older individuals. Sometimes the post-recovery period may be marked by fatigue (Moya et al, 2009).

The adjective 'pre-syncopal' is used to indicate symptoms and signs that occur before unconsciousness in syncope, so its meaning is literal when used in this context and making it a synonym of 'warning' and 'prodromal'. The noun 'pre-syncope' or 'near-syncope' is used often to describe a state that resembles the

prodrome of syncope but which is not followed by TLOC; doubts remain as to whether the mechanisms involved are the same as in syncope (Moya et al, 2009).

1.3 Causes of syncope

The final pathophysiological pathway behind syncope is sudden transient global cerebral hypoperfusion. Thus, conditions that reduce cardiac output (CO) and cause excessive vasodilatation can cause syncope. The pathophysiological classification of the principal causes of syncope is shown in Table 1.1.2 (Moya et al, 2009).

Reflex (neurally-mediated) syncope

- Vasovagal
  - Mediated by emotional stress (e.g. fear, pain, instrumentation, blood phobia etc.)
  - Mediated by orthostatic stress
- Situational
  - Cough, sneeze, Gastrointestinal stimulation (Swallow, defecation, visceral pain), micturition, post-exercise, postprandial
  - Others (e.g. Laugh, brass instrument player etc.)
- Carotid sinus hypersensitivity related syncope

- Atypical forms (Without apparent triggers and/or atypical presentation)

Syncope due orthostatic hypotension / orthostatic intolerance syndromes

- Primary autonomic failure
  - Pure autonomic failure, multiple system atrophy, Parkinson's disease with autonomic failure and Lewy body dementia.
- Secondary autonomic failure
  - Diabetes, amyloidosis, uremia, spinal cord injuries
- Drug induced orthostatic hypotension
  - Alcohol, vasodilators, diuretics, phenotiazines, antidepressants
- Volume depletion
  - Hemorrhage, diarrhea, vomiting etc.

Cardiac syncope

- Arrhythmia as primary cause
  - Bradycardia
    - Sinus node dysfunction, atrioventricular conduction system disease, implanted device malfunction (e.g. Pacemaker)
  - Tachycardia
    - Supraventricular (SVT), Ventricular (VT)
  - Drug induced tachycardia / Bradycardia
- Structural heart disease
  - Cardiac:
    - Valvular disease, acute myocardial infarction/ischemia,

Hypertrophic cardiomyopathy, cardiac masses, pericardial disease/tamponade, congenital abnormalities of coronary arteries, prosthetic valve dysfunction ➢ Others: Pulmonary embolism, acute aortic dissection, pulmonary hypertension

Table 1.1.2: Classification of syncope

A distinction along pathophysiological lines centres on a fall in systemic blood pressure (BP) (Systolic BP = 60 mmHg or lower) with a decrease in global cerebral blood flow as the basis for a syncopal event. A sudden cessation of cerebral blood flow, for as short as 6–8 seconds, has been shown to be sufficient to cause complete TLOC. CO and total peripheral vascular resistance determine systemic BP, and a fall in either can cause syncope, but a combination of both mechanisms is often present, even if their relative contributions vary considerably. Moreover, a low or inadequate peripheral resistance can be due to inappropriate reflex activity causing vasodilatation and bradycardia manifesting as vasodepressor, mixed, or cardioinhibitory reflex syncope. Other causes of a low or inadequate peripheral resistance are functional and structural impairments of the autonomic nervous system (ANS) with drug-induced, primary and secondary autonomic failure (ANF). In ANF, sympathetic vasomotor pathways are unable to increase total peripheral vascular resistance in response to the

upright position. Gravitational stress, in combination with vasomotor failure, results in venous pooling of blood below the diaphragm, causing a decrease in venous return and consequent decrease in CO. Furthermore, the main causes of transient low CO are 3-fold. The first is a reflex causing bradycardia, known as cardioinhibitory type of reflex syncope. The second is cardiovascular causes, due to arrhythmia and structural disease including pulmonary embolism/hypertension. The third is inadequate venous return due to volume depletion, acute hemorrhage or venous pooling (Moya et al, 2009).

1.3.1 Reflex syncope (Neurally mediated syncope)

Reflex syncope traditionally refers to a heterogeneous group of conditions (See Table 1.1.2) in which cardiovascular reflexes that are normally useful in controlling the circulation become intermittently inappropriate, in response to a trigger, resulting in vasodilatation and/ or bradycardia and thereby in a fall in arterial BP and global cerebral perfusion (van Dijk et al, 2008).

Reflex syncope may also be classified based on its trigger, i.e. the afferent pathway including (Moya et al, 2009): "Vasovagal syncope" (VVS), also known as "neurocardiogenic syncope" and 'common faint', mediated by emotion or by

orthostatic stress. It is usually preceded by prodromal symptoms of autonomic activation (sweating, pallor, nausea) that can progress to TLOC.

Situational syncope traditionally refers to reflex syncope associated with some specific circumstances such as acute stress (i.e. seen blood and panic attacks) coughing, sneezing, gastrointestinal stimulation (i.e. swallowing) and micturition.

Post-exercise syncope can occur in young athletes as a form of reflex syncope as well as in middle-aged and elderly subjects as an early manifestation of autonomic dysfunction before they experience typical orthostatic hypotension (OH).

Carotid sinus syncope deserves special mention. In its rare spontaneous form it is triggered by mechanical manipulation of the carotid sinuses. In the more common form no mechanical trigger is found and it is diagnosed by carotid sinus massage (CSM).

Finally, the term 'atypical form' is used to describe those situations in which reflex syncope occurs with uncertain or even apparently absent triggers. The diagnosis then rests less on history taking alone, and more on the exclusion

of other causes of syncope (absence of structural heart disease) and on reproducing similar symptoms with tilt testing. Such less clear presentations may overlap with clear-cut occurrences within patients.

1.3.2 Orthostatic hypotension and orthostatic intolerance syndromes

In contrast to reflex syncope, in ANF sympathetic efferent activity is chronically impaired so that peripheral vasoconstriction is deficient. Upon standing, BP falls and syncope or pre-syncope occurs. OH is defined as an abnormal progressive decrease in systolic BP upon standing. On the other hand, orthostatic intolerance refers to symptoms and signs in the upright position due to a circulatory abnormality (Moya et al, 2009). Classical OH is a physical sign defined as a decrease in systolic BP ≥20 mmHg and in diastolic BP ≥10 mmHg within 3 minutes of standing (Moya et al, 2009) described in patients with pure ANF, hypovolemia, or other forms of ANF. Initial OH is characterized by a BP decrease immediately on standing of > 40 mmHg (Wieling et al, 2007). BP then spontaneously and rapidly returns to normal, so the period of hypotension and symptoms is short (<30 seconds). Delayed (slow progressive decrease in systolic BP) OH (Gibbons et al, 2006) is not uncommon in elderly persons that is attributed to age-related impairment of compensatory reflexes and stiffer hearts in the elderly sensitive to a decrease in preload. Finally, in some patients mostly

young woman, Postural orthostatic tachycardia syndrome' (POTS), presents with severe complaints of orthostatic intolerance, but not syncope, with very marked heart rate (HR) increases ≥30 beats per minute (bpm) or to >120 bpm and instability of BP during the orthostatic stress or standing.

1.3.3 Cardiac syncope

Arrhythmias are the most common cardiac causes of syncope including: bradycardia (Sinus node dysfunction, atrioventricular conduction system disease, implanted device malfunction), tachycardia (supraventricular and ventricular) as well as drug or metabolic induced bradycardia and tachycardia. They induce hemodynamic impairment, which can cause a critical decrease in CO and significant drop in cerebral blood flow. Nonetheless, syncope often has multiple contributory factors, including HR, type of arrhythmia, left ventricular function, posture and adequacy of vascular compensation (Moya et al, 2009). Regardless of such contributing effects, when an arrhythmia is the primary cause of syncope, it should be specifically treated.

On the other hand, structural cardiac diseases can cause syncope when circulatory demands outweigh the impaired ability of the heart to increase its output. Table 1.1.2 lists the most frequent cardiovascular diseases that can

cause syncope. Syncope is of great concern when it is associated with conditions in which there is fixed or dynamic obstruction to left ventricular outflow such as aortic stenosis or hypertrophic cardiomyopathy. The basis for the TLOC is inadequate blood flow due to mechanical obstruction at cardiac level. To recognize the heart as the cause of the problem is justified by the need to correct the underlying structural disease, when possible.

1.4 Epidemiology and burden of syncope

Syncope is common in the general population accounting to 1% to 3% of emergency department (ED) annual visits as well as 6% of hospital admissions in North America (ACEP, 2001; Huff et al, 2007). Similarly, recent data reported a remarkably constant frequency of syncope in community-based EDs in Europe, with an incidence of >1% of all attendances (range 0.9–1.7%) (Moya et al, 2009). The Framingham Offspring Study estimated that 42% of all participants (mean age 51 years range 20–96 years) suffered at least one syncopal episode during a follow-up of 17 years (Soteriades et al, 2002)..

Recently, investigators (Sun et al, 2005), using a representative sample of hospital discharges (7,450,992 discharges from 994 hospitals) in the United States reported a conservative estimate of total annual costs for syncope-related

hospitalizations of $2.4 billion (95% Confidence Interval (CI), $2.2 to $2.6 billion), with a mean cost of $5,400 (95% CI, $5,100 to $5,600) per hospitalization Efforts to safely decrease syncope-related admissions may result in substantial costs savings.

Finally, recurrent syncope has serious effects on quality of life (QOL). The physical impairment due to syncope is comparable with chronic illnesses such as chronic arthritis, recurrent moderate depressive disorders, and end-stage renal disease (Moya et al, 2009). Moreover, in patients with frequent recurrent syncope, psychosocial impairment had an estimated average adverse impact on 33% of the assessed aspects of daily life. Syncope reduces mobility, usual abilities, and self-caring, and increases depression, pain, and discomfort. Female gender, high level of co-morbidity, number of episodes of syncope, and presence of pre-syncope seemed to be associated with poorer QOL (van Dijk et al, 2006).

1.5 Prognosis

With regard to the prognosis (i.e. risk stratification) associated with syncope, two important elements should be considered: (1) risk of death and life-threatening events; and (2) risk of recurrence of syncope and physical injury.

According to the Framingham Offspring study (Soteriades et al, 2002), the multivariable-adjusted hazard ratios among participants with syncope from any cause compared with those who did not have syncope were 1.31 (95% CI, 1.14 to 1.51) for death from any cause, 1.27 (95% CI, 0.99 to 1.64) for myocardial infarction or death from coronary heart disease and 1.06 (95% CI, 0.77 to 1.45) for fatal and non fatal stroke. Cardiac syncope was associated with increased one-year mortality rate (18 to 33%) while it was lower for non-cardiac syncope (0 to 12%). Furthermore, cardiac syncope is an independent predictor of mortality and sudden cardiac death (SCD). The SCD death rate was 24% in the cardiac syncope group and 3-4% in the non-cardiac and unexplained syncope groups (Kapoor et al, 1996). Patients with advanced heart failure (ejection fraction ≤20%) and syncope had a higher risk of SCD at one-year regardless of the etiology of syncope (Middlekauff et al, 1993). Conversely young healthy syncope patients with normal 12 lead electrocardiogram (ECG) and no structural heart disease, patients with neurally mediated syncope and patients with orthostatic hypotension due to transient problems (such as volume depletion, drug induced) had excellent prognosis (Soteriades et al, 2002). Thus, occurrence of syncope in those with pre-existing medical conditions is associated with significant morbidity and mortality.

1.6 Assessment of syncope in the Emergency Department

1.6.1 Initial evaluation

The initial evaluation of a patient presenting with syncope to the ED consists of careful history, a complete physical examination, including orthostatic BP measurements, and an ECG. Based on specific findings in this initial assessment, additional examinations may be performed, including: Carotid Sinus Massage (CSM) in patients >40 years, echocardiogram when there is previous known history of heart disease or data suggestive of structural heart disease or syncope secondary to cardiovascular cause, immediate ECG monitoring when there is a suspicion of arrhythmic syncope and orthostatic challenge (lying-to-standing orthostatic test and/or head-up tilt testing) when syncope is related to the standing position or there is a suspicion of a reflex mechanism. Other less specific tests such as neurological evaluation or blood tests are only indicated when there is suspicion of non-syncopal TLOC (Moya et al, 2009).

Thus, the initial evaluation should answer three key questions: 1) is it a syncopal episode or not? 2) Has the etiological diagnosis been determined? And, 3) are there data suggestive of a high risk of cardiovascular events or death?

1.6.2 Diagnosis of syncope

The differentiation between syncope and non-syncopal conditions with real or apparent TLOC as well as the etiology of syncope can be achieved in most cases with a detailed initial evaluation permitting no further evaluation and the institution of immediate treatment.

During the initial evaluation of TLOC, the following questions should be answered: (1) Was TLOC complete? (2) Was TLOC transient with rapid onset and short duration? (3) Did the patient recover spontaneously, completely without persistent neurological deficit? (4) Did the patient lose postural tone? If the answers to these questions are positive, the episode has a high likelihood of being syncope. If the answer to one or more of these questions is negative, exclude other forms of TLOC before proceeding with syncope evaluation (Moya et al, 2009).

1.6.3 Risk stratification

When the cause of syncope remains uncertain after initial evaluation the next step is to assess the risk of major cardiovascular events or SCD. The main high-risk features, in accordance with recent guidelines on SCD (Goldberger et al, 2008) and cardiac pacing (Epstein et al, 2008) are listed in Table 1.1.3.

Severe structural or coronary disease • Heart failure / Low LVEF • Previous history of myocardial infarction
Clinical and ECG features suggesting arrhythmic syncope • Syncope during excursion or supine position • Palpitations at the time of syncope • Family history of SCD • Non-sustained VT • Bifascicular conduction block • Inadequate sinus bradycardia (HR<50) or sinoatrial block • Pre-excited QRS complex • Prolonged or short QT interval • Right Bundle Branch Block (RBBB) pattern with ST elevation in leads V1 to V3 (Brugada pattern) • Negative T waves in right precordial leads, epsilon waves and ventricular late potentials suggestive of Arrhytmogenic right ventricular cardiomyopathy (ARVC)
Important comorbidities • Severe anemia • Electrolyte disturbances

Table 1.1.3: Short-term high-risk criteria, which require prompt hospitalization or intense evaluation

Once the cause of TLOC is found after initial evaluation in the ED, then treatment is directed towards the etiology of syncope. Thus, if the cause is benign most patients can be safely discharged home from the ED. However, in a substantial proportion of patients a cause cannot be found and they pose a huge management dilemma to the emergency physician as they may be at risk for serious outcomes after discharge and they need admission to hospital. ED based syncope studies report that 31% to 54% of patients do not have a cause identified even after full evaluation (Sarasin et al, 2001). The OESIL risk score found that high-risk patients have a mortality rate as high as 57.1% within the first year (Colivicchi et al, 2003). Moreover, among the ED syncope patients, 9%-14% will suffer serious outcomes (include death, myocardial infarction, arrhythmia, pulmonary embolism, stroke, subarachnoid hemorrhage, significant bleeding) within 30 days of their visit with about 50% of these occurring after ED discharge (Quinn et al, 2004; Quinn et al, 2006; Sun et al, 2007).

In summary, the evaluation of syncope in the setting of ED has changed from attempts to make a diagnosis of the cause of syncope to risk stratification in order to: (1) recognize patients with life-threatening conditions and admit them to the hospital; (2) recognize patients with low risk conditions to be discharged and referred later to local syncope facilities; (3) recognize those who do not need any

further evaluation and treatment; and (4) choose a timing and setting where further diagnostic tests should be performed in patients with inconclusive initial evaluation (Moya et al, 2009).

1.6.4 Evidence based risk stratification tools and clinical decision rules

Several different studies have analyzed the impact and prognosis of clinical data on the follow-up of patients with syncope presenting to the ED using risk stratification tools and decision rules. A synopsis of the available evidence based on clinical decision rules and risk stratification tools and how they perform in the clinical setting is given below:

1.6.4.1 The San Francisco Syncope Rule (SFSR)

The SFSF was derived from a prospective cohort study conducted at a university teaching hospital in ED patients presenting with syncope or near syncope (1.4% of 58.884 ED visits) to identified patients at risk for short-term serious outcomes at 7 days and subsequently validated for serious outcomes at 30 days (Quinn et al, 2004; Quinn et al, 2006). Both the derivation and validation phases reported a sensitivity of 96-98% and specificity of 56-62%. The rule had the potential to decrease admission to hospital by 7-10%. The variables in the rule are: (1) Systolic BP at the time of triage less than 90 mmHg, (2) patient

complain of shortness of breath, (3) history of congestive heart failure, (4) ECG abnormalities (non-sinus rhythm or any new changes) and hematocrit less than 30% (See Appendix 1 for details). Thus, no- risk is defined as a score < 1 and high risk as ≥ 1.

There are wide variations in the performance of the rule across different validation studies with sensitivity varying from 69% to 100% and specificity from 33% to 57% (Birnbaum et al, 2008; Cosgriff et al, 2007; Reed et al, 2007; Sun et al, 2007). In a retrospective Canadian study, the SFSR performed with comparable sensitivity but significantly poorer specificity than previously reported (Thiruganasambandamoorthy et al, 2010). The rule performed with a sensitivity of 90% (44/49 outcomes; 95% CI [79% to 96%]) and a specificity of 33% (95% CI 32% to 34%). Including monitor abnormalities in the ECG variable would improve sensitivity to 96% (47/49 outcomes; 95% CI [87% to 99%]). Moreover the SFSR was able to predict all 3 deaths that occurred after ED discharge in this cohort. However, the implementation of the rule in the Canadian setting increases the admission rate from 12.3% to 69.5%.

The SFSR investigators have stated that failure to validate the decision rule in other cohorts has been related to with selection bias in the inclusion of

patient as well as wrong interpretation and application of the rule regarding specifically abnormal ECG (McDermott et al, 2009). Based on methodological standards the SFSR is one of the instruments that is prospectively derivated, prospectively validated and included all serious outcomes in the short-term analysis.

1.6.4.2 OESIL (Osservatorio Epidemiologico sulla Sincope nel Lazio) Risk Score

The OESIL risk score (Colivicchi et al, 2003) was prospectively derivated and validated from a cohort of patients (270) presenting to the ED with syncope to predict only total mortality within 12 months. The variables included in the model are (1) age > 65 years, (2) cardiovascular disease in clinical history, (3) syncope without prodrome and (4) abnormal ECG. One point is given for each variable. The twelve-month all cause mortality in the derivation cohort according to the score was: 0=0%, 1=0.1%, 2=19.6%, 3=34.7% and 4=57.1%. A similar pattern of increasing mortality with increasing score was prospectively confirmed in a second validation cohort of 328 consecutive patients: 0=0%, 1=0.6%, 2=14%, 3=29% and 4=53%. Thus, patient with OESIL score from 0 to 1 can be discharged home safely, avoiding unnecessary hospitalizations to hospital. The authors concluded that the OESIL risk score might represent a simple

prognostication tool that could be usefully employed for the triage and management of patients with syncope in ED.

1.6.4.3 European Society of Cardiology Guidelines on Management (Diagnosis and Management) of Syncope

The ESC guidelines are based on expert opinion and they recommended admission to hospital of those patients with significant heart disease, abnormal ECG, syncope during exercise or while supine, associated severe injury, family history of sudden death, preceding palpitations, frequent recurrent episodes or high suspicion of cardiac syncope, and also of those who require treatment of arrhythmias, cardiopulmonary or neurological disorders or pacer insertion (Brignole et al, 2001; Brignole et al, 2004a; Brignole et al, 2004b). Moreover, the 2009 updated ESC guidelines added severe anemia and electrolyte disturbance as admission to hospital criteria for patients presenting with syncope in the ED (Moya et al, 2009). Overall, the guidelines are based more on expert opinion than evidence. Moreover these guidelines were not been prospectively derivated or validated, since they are not based on original clinical research. Nevertheless, they offer a good learning and reviewing tool for the clinician facing the assessment of syncope in the ED.

1.6.4.4 Risk stratification of syncope in the emergency department study (ROSE)

The ROSE study (Risk stratification of syncope in the emergency department) was a single centre prospective, observational study (Reed et al, 2010) that validated a clinical decision rule (CDR) to predict 1-month serious outcome and all-cause mortality in patients presenting with syncope to ED. The CDR was devised from 550 patients in a derivation cohort and tested in a validation cohort of a further 550 patients. One-month serious outcomes or all-cause death occurred in 40 (7.3%) patients in the derivation cohort. Independent predictors were brain natriuretic peptide concentration > 300 pg/ml (Odds Ratio (OR): 7.3), positive fecal occult blood (OR: 13.2), hemoglobin < 90 g/L, (OR: 6.7), oxygen saturation < 94% (OR: 3.0) and Q wave on presenting ECG (2.8). One-month serious outcome or all-cause death occurred in 39 (7.1%) patients in the validation cohort. The ROSE-CDR had a sensitivity and specificity of 87.2% and 65.5%, respectively, and a negative predictive value of 98.5%. An elevated B-type natriuretic peptide (BNP) concentration alone was a major predictor of serious cardiovascular outcomes (8 of 22 events, 36%) and all-cause deaths (8 of 9 deaths, 89%). Unfortunately, the BNP is not universally available in Canada and some provinces such as Ontario did not have access to the test in the

general clinical practice. Thus, using the ROSE rule in the RESASTER-SCP would be inconvenient since the validity of the rule will be compromised. Moreover, ROSE investigators (Reed et al, 2011) examined the incidence of adverse events at 1 year in the cohort of ED syncope patients enrolled in the original study and found out that the instrument does not perform well at predicting 1-year outcomes in this population.

1.6.4.5 Other instruments

Martin et al (Martin et al, 1997) developed the very first risk stratification system to predict arrhythmias or deaths in ED syncope patients at 1-year. The predictors were abnormal ECG, ventricular arrhythmia, previous history of CHF or age >45 years. The instrument was limited since it only predicted arrhythmia or death and required all patients over 45 years to be admitted to hospital. For that reason, is not currently used by emergency physicians.

The American College of Emergency Physicians (ACEP) clinical policies released in 2001 (ACEP, 2001) and revised in 2007 (Huff et al, 2007) do not attempt to outline the evaluation of patients presenting with syncope associated with specific diagnoses but rather focus on assisting the emergency physician in addressing 3 critical questions: 1) What history and physical examination data

help to risk stratify patients with syncope?; 2) What diagnostic testing data help to risk-stratify patients with syncope? And 3) who should be admitted after an episode of syncope of unclear cause? In conclusion, the factors that lead to stratification as high-risk for adverse outcomes are: Older age and associated comorbidities (it can reflect the cardiovascular health of an individual), abnormal ECG (including acute ischemia, arrhythmias or significant conduction abnormalities), Hct < 30 (if obtained) and history or presence of heart failure, coronary artery disease or structural heart disease

Finally, Sarasin's (Sarasin et al, 2001) assessed the diagnostic yield of a standardized sequential evaluation of patients presenting with syncope to the ED. Abnormal ECG, history of congestive heart failure and age >65 years old predicted arrhythmias in this cohort of patients. Investigators concluded that when patients have unexplained syncope, cardiovascular testing for detecting arrhythmias should be reserved for those with abnormalities on baseline ECG, whether or not they have underlying heart disease.

1.6.5 Syncope management unit

A cohesive, structured care pathway delivered either within a dedicated syncope facility or as a more multifaceted service, is optimal for quality service delivery. Furthermore, considerable improvement in diagnostic yield and cost

effectiveness (i.e. cost of hospitalization and investigations) can be achieved (Moya et al, 2009). Any syncope (TLOC) facility is aimed at reaching the following goals: (1) Provide state-of-the-art guideline-based assessment of symptomatic patients in order to risk-stratify them, then obtain an accurate etiological diagnosis and assess prognosis; (2) Physician(s) in charge of the syncope facility lead the process of comprehensive management from those listed above to therapy, and, if necessary, follow-up. They perform the core laboratory tests and have preferential access to hospitalization, diagnostic tests, and therapeutic procedures; (3) Reduce hospitalizations. The majority of patients can be investigated as out patients or day cases and (4) Set standards for clinical excellence in adherence to the recommendations on syncope.

In the Evaluation of Guidelines in Syncope Study 2 (EGSYS-2) (Brignole et al, 2006) (Del Rosso et al, 2008), the implementation of a standardized decision making approach was facilitated by a computer software based on the ESC Guidelines for the diagnosis of syncope in 19 Italian hospitals. Core medical personnel (syncope unit) were designated—both locally in each hospital and centrally—to verify adherence to the diagnostic pathway and give advice on its correct application. Investigators demonstrated that 78% of study subjects adhered to the guideline-based evaluation, resulting in a lower hospitalization

rate (39% vs. 47%), shorter in-hospital stay (7.2+5.7 vs. 8.1+5.9 days), and fewer tests performed per patient (median 2.6% vs. 3.4) than historical controls.

The only randomized study evaluating efficiency and accuracy of the investigation of syncope with a dedicated syncope clinic/unit is the SEEDS trial (Shen et al, 2004). This study allocated 103 intermediate-risk syncope patients presenting to a single centre to a standard care approach compared to a syncope unit evaluation associated with the ED. The unit provided 6 hours of ECG monitoring, echocardiography, an urgent head up tilt test, and an arrhythmia consult. Diagnostic yield was significantly higher in those patients randomized to the syncope unit arm (67% vs. 10%), mostly due to increased detection of vasovagal syncope. Hospital admission rates were lower in the syncope unit group (43% compared to 98% in the standard of care group). There were no differences in total mortality or syncope recurrence.

1.7 Diagnosis of Syncope in the Emergency Department: A Systematic Review of Literature

A comprehensive systematic review of the literature was performed to summarize the current evidence associated to the diagnosis of syncope in the emergency department. The search strategy incorporated medical subject

headings (MeSH) and subheadings words from the MEDLINE database from the U.S National Library of Medicine / National Institutes of Health (1966 to July 2011). The MeSH word "syncope", defined as transient loss of consciousness and postural tone caused by diminished blood flow to the brain, and the subheading "syncope diagnoses" were linked to the MeSH word "Hospital Emergency Service" defined as the Hospital department responsible for the administration and provision of immediate medical or surgical care to the emergency patient, for the PUBMED search. No language restrictions were applied to the search strategy. Sixty-five articles were the result of this search. Subsequently, the search was limited to systematics reviews and meta-analysis. Three methodological well-designed systematic reviews were used as main reference for the rationale of RESASTER study:

The first article reported by Serrano et al (Serrano et al, 2010) assessed the methodological quality and prognostic accuracy of clinical decision rules in emergency department syncope patients and identified 18 eligible studies. Deficiencies in outcome (blinding) and inter-rater reliability assessment were the most common methodological weaknesses. Thus, authors conclude that the methodological quality and prognostic accuracy of clinical decision rules for syncope are limited. For instance, differences in study design and ECG

interpretation may account for the variable prognostic performance of the San Francisco Syncope Rule when validated in different practice settings.

The Canadian Cardiovascular Society (CCS) has published a position paper describing a standardized approach for syncope diagnosis (Sheldon et al, 2011). Difficulties in the delivery of health services can be improved by standardized approaches, including guidelines, pathways, and checklists. Accordingly, ED syncope decision rules, specialized syncope-monitoring units, and formal diagnostic algorithms have all been developed to provide standardized approaches to the investigation of syncope. The goals of the CCS systematic review were to summarize the evidence and its quality and to make recommendations on whether any of the 3 approaches for the diagnosis of syncope merit adoption at this time. The Writing Panel searched PubMed and found 979 articles of interest and then added articles identified by hand searches of personal files and reference lists. This list was narrowed to 85 based on examination of the title or abstract and on discarding letters and duplicates. Other articles from outside the field were added as necessary. The panel reviewed the current status of the field, asked whether the published work posed a significant improvement over current practice, and made observations and recommendations using the GRADE format. Briefly, GRADE uses a structured

method to weigh the quality of the evidence and a similarly structured method to describe the strength of the recommendation or observation (Guyatt et al, 2008). Finally, a secondary panel reviewed the resulting document, and it then was submitted to the CCS Guidelines Committee. Overall, the position group concluded that there is little persuasive evidence that emergency department syncope rules and diagnostic syncope units provide efficient care and improved outcomes but that formal diagnostic algorithms with specialist support show promise (Sheldon et al, 2011). Canadian Cardiovascular Society recommendations are summarized as follows:

- Higher-risk patients, who should be considered for further assessment, are those with at least one major risk factor (History or presence of congestive heart failure, an abnormal ECG, structural heart disease, and hypotension **<** 90 mm Hg systolic) (Strong Recommendation, Low-Quality Evidence).
- Existing syncope decision rules do not increase diagnostic specificity or sensitivity, or reduce costs (Weak Recommendation, Very Low-Quality Evidence).

- Formal syncope units might increase diagnostic specificity or sensitivity, and reduce costs (Weak Recommendation, Low-Quality Evidence).
- Standardized diagnostic testing pathways may improve efficiency and reduce unnecessary testing, if risk factor stratification for short term outcomes is formally implemented (Strong Recommendation, Low-Quality Evidence)

Finally, the ESC published in 2009 the revised Guidelines for the diagnosis and management of Syncope (Moya et al, 2009). The first aim of this guideline was to stress the concept that there are two distinct reasons for evaluating patients with syncope: one is to identify the precise cause in order to address an effective mechanism specific treatment; the other is to identify the specific risk to the patient, which frequently depends on the underlying disease rather than on the mechanism of syncope itself. The second objective was to produce a comprehensive document, which is addressed not only to cardiologists but also to all physicians who are interested in the field. In order to achieve this aim a great number of other specialists were involved, as either full members, external contributors, or reviewers nominated by international societies of neurology, autonomic disease, internal medicine, emergency medicine, geriatrics,

and general medicine. In total 76 specialists from different disciplines participated in the project.

In conclusion, there is weak evidence supporting the role of standardized care pathways in the diagnosis of syncope in the ED. Randomized control trials are necessary to support the current evidence that those interventions improve quality of care and patients outcomes.

Chapter 2 RESASTER Study Design Considerations

2.1 Introduction

This chapter discusses study rationale (section 2.2), study hypothesis (section 2.3), study objectives (section 2.4), selecting study design (section 2.5), RESASTER-SCP description (section 2.6), cluster definition and eligibility (section 2.7), the unit of inference (section 2.8), participant recruitment (section 2.9) and randomization procedures (section 2.10).

Since the purpose of this protocol is the evaluation of a structured care pathway that will be applied in the ED across the country changing professional behaviours regarding admission to hospital, it is not practical to simply randomize patients for comparison and analysis. For that reason the cluster randomized control trial design has been selected to provide an unbiased answer to the research question (Internal validity). Additionally, it will allow applying the study results to a broader population improving the external validity of the study. Finally, the importance of minimizing commission and omission errors, defined as admitting low risk patient and failing to admit a high-risk patient to hospital respectively is a key factor in order to minimize bias and affect the results of the study.

2.2 Study rationale

A cohesive, structured care pathway, delivered either within a single syncope facility or as a more multifaceted service, is recommended for global assessment of patients presenting to ED with syncope. Referral can be directly from: family practitioners, ED, acute hospital inpatients, institutional settings. The objectives of a structured care pathway for syncope diagnosis are:

(1) Provide the patient with continuity of care

(2) Reduce inappropriate hospitalizations

(3) Set standards of clinical excellence in the field. Moreover, experience and training in key components of internal medicine, cardiology, neurology, emergency and geriatric medicine are pertinent to apply the structured care pathway (Moya et al, 2009)

Despite, admission rates to hospital of ED syncope patients are much lower in Canada than in US studies (Thiruganasambandamoorthy V, 2008), a significant proportion of patients (10%) can suffer adverse outcomes after discharge. There is a need for an accurate clinical decision rule to guide

admission to hospital for patients presenting with syncope to the ED at high risk adverse outcomes. This will improve patient safety and will also guide the ED physician and other specialist to a rapid disposition of patients. Moreover, the cost of the syncope assessment will be reduced. Different decision rules and risk stratification scores have been proposed but they have not been systematically compared versus the conventional approach in a prospective cluster randomized trial.

2.3 Study Hypotheses

The RESASTER-SCP, applied to patients presenting to the ED with syncope, will prevent unnecessary admissions to the General Hospital without increasing important outcomes, such as re-admission, death, cardiovascular morbidity etc.

2.4 Study Objectives

2.4.1 Primary objective

To determine whether the RESASTER-SCP is superior to usual care in identifying patients at low risk for serious outcomes presenting to the ED with syncope who can be safely discharged home.

2.4.2 Secondary objectives

- To determine whether the RESASTER-SCP is superior to usual care in identifying patients at high risk for serious outcomes presenting to the ED with syncope who required immediate admission to the General Hospital.

- To determine whether the RESASTER- SCP compared to usual care improves the diagnostic yield in patients presenting with syncope to the ED in the General Hospital.

2.5 Selecting study design: Cluster Randomized Trial

Cluster randomized trials are characterized by the randomization of groups (clusters) of patients rather than individuals (Fayers et al, 2002). This type of design is used to measure the effects of health care interventions and educational strategies, which by their nature are applied to entire communities or other groups of individuals (organizational units). In this instance it would be impractical or inadequate to randomize individual patients. Instead, in order to evaluate the intervention, one must randomize higher-level units. Thus, in RESASTER Study, EDs across the province of Ontario in Canada represent a cluster of patients that offer greater logistical convenience for the application of a

SCP. Moreover, randomization by cluster is used to avoid 'contamination' between treatment groups. Contamination usually refers to a situation where individuals in one treatment arm actually receive part or all of the intervention allocated in the other arm. Thus, if some patients in the ED were randomly allocated to receive RESASTER-SCP, it would be difficult to prevent physicians applying the experimental strategy to conventional strategy group through communication with other physicians in the same institution, or in a worse situation, some physicians tempt applying an "assumed better strategy" in the control group unintentionally (Fayers et al, 2002). The result of contamination is that the outcome differences between the treatments arms will be regressed toward null hypothesis and then diluted, biasing the trial towards smaller effect estimates (or finding no difference). Moreover, the effect of clustering may be particularly strong in health care trials where between-cluster variation will then reflect variations in the responses of individual practitioners that will require a higher number of clusters to compensate, as well as variation due to differences among patients. In this study, EDs will be randomized to apply the RESASTER-SCP or the conventional usual care strategy currently applied by physicians based on clinical judgment. The design of the RESASTER Study is graphically depicted in Figure 2.1.

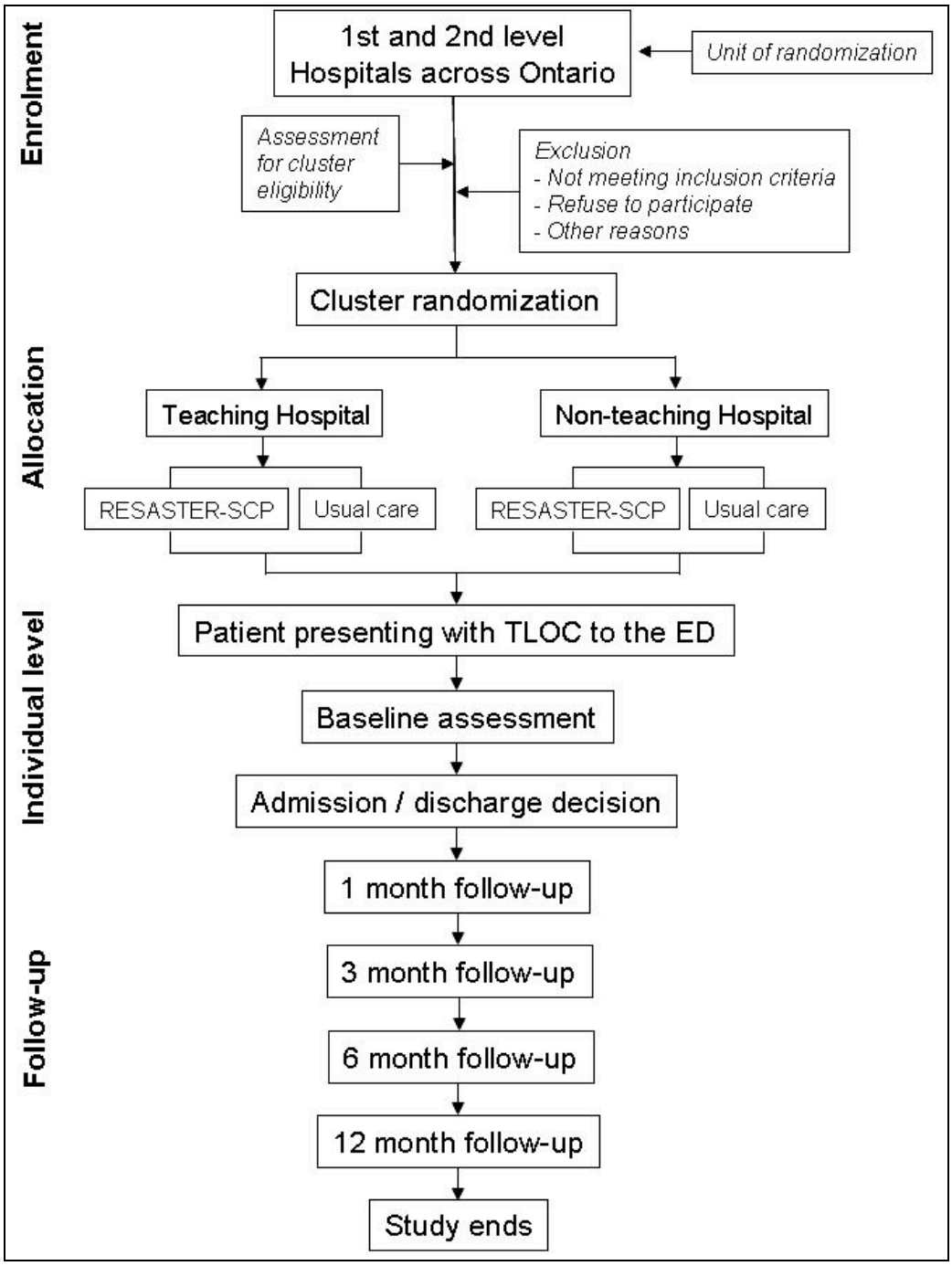

Figure 2.1 Schematic representation of RESASTER study

2.5.1 Disadvantages and limitations of cluster randomization

While cluster randomization offers important advantages, these need to be weighed against a number of limitations and disadvantages of this study design, as follows (Hayes et al, 2009).

2.5.1.1 Efficiency

As a result of between-cluster variability (see chapter 4 for details), the power and precision of a cluster-randomized trial will generally be lower than for an individual randomized trial of the same size. Thus, if there are large clusters or there is a substantial variability between clusters, the design effect may be considerable, so the cluster randomized trial design is more costly. The statistical and cost efficiency of a cluster-randomized needs to be carefully considered when choosing between alternative study designs (Hayes et al, 2009).

2.5.1.2 Selection bias

Selection bias refers to any effect causing the sample estimate to deviate systematically from the true population values. Selection bias at the enrolment stage may be a particularly serious concern for some types of cluster randomized trials when medical practices are randomly allocated to implement two strategies to diagnose or treat patients with a specific condition. Because the study arm is

already known, both doctors and patients will be aware of the intervention that will be implanted if the patient is enrolled. Depending on prior opinions of the different medical strategies and belief about their efficacy, the doctor or patient may be influenced in their decisions regarding enrolment and this may lead to significant selection bias. In RESASTER Study selection bias will be reduced using transparent and objective criteria for patient enrolment that are agreed by all participating clusters prior to randomization. This will be combined with regular visits by trial monitors to check medical records at each practice to ensure that all patients meeting the agreed inclusion criteria have been invited to enrol. (Hayes et al, 2009)

2.5.1.3 Imbalance between study arms

As a result of practical and financial constraints, the number of clusters randomized in a cluster-randomized trial is often quite small. With a small number of randomization units, it is quite likely that there will be some imbalance on one or more potential confounding factors, and there is no question that the credibility of the trial results may be weakened in the presence of such imbalances (Hayes et al, 2009). For RESASTER Study, design strategies including randomization and sequence generation will be used in an attempt to avoid imbalances between arms. There are described below in this chapter (section 2.10).

2.5.1.4 Generalizability

Special attention will be given to the generalizability of cluster randomized trials. When results are reported, it is common to consider to what extent their results are generalizable to a wider target population, or to population in different geographical settings. Community and practice level interventions are often complex and operate on endpoints through an elaborated web of cause and effect. Thus, these interventions may show much more variation than interventions on individual subjects for several reasons: 1) Community and practice level interventions are less clearly defined than patient interventions, and are likely to differ in their *implementation* in different settings; 2) the *response* to complex interventions may also show considerable variation between populations, particularly where they involve behaviour change and 3) the *indirect effects* of interventions may vary substantially between populations because of differences in characteristics of individuals in those populations (Hayes et al, 2009).

2.6 RESASTER-SCP

Based on previous literature and validated data the RESASTER-SCP has been designed using the SFSR (Quinn et al, 2004; Quinn et al, 2005; Quinn et al,

2006) and OESIL (Colivicchi et al, 2003) for the intervention arm of the study. Detailed description of this two decision rules has been presented in chapter 1 (See section 1.6.4.1 and 1.6.4.2 respectively). Moreover, RESASTER-SCP would include a detailed clinical history and focus physical exam as well as standard 12-ECG and basic blood work (Cell blood count, sodium, potassium, chloride, magnesium, phosphate, calcium, albumin, creatinine, urea, ALT, AST, Bilirubin, INR and PTT) as part of the initial assessment in the standardized pathway. Pre-printed forms of the SFSR and OESIL will be distributed to clusters (ED) randomized to the intervention to be applied by the most responsible physician during the assessment of the patient in the ED. The idea of using two independent decision rules is to protect high-risk patients that required immediate admission to hospital and should not be discharged home, in order to prevent an omission error (see section 5.3). Thus, if both of decision rules are positive, patient will be admitted to hospital for further assessment and treatment. Similarly, if one of the two decision rules is positive for admission to hospital and the other one is negative, patient will be admitted to hospital regardless. On the contrary if both decision rules are negative for admission to hospital the clinician will discharge the patient home with pertinent follow-up defined by the primary care giver or the most responsible physician as well as the RESASTER research assistants. All the physicians in the intervention clusters will be trained by the

investigators in how to use and applied the RESASTER-SCP before starting the study. This will be operationalized and also will require a precise documentation of the received training.

2.7 Cluster definition and eligibility

One of the first decisions to be made when designing a cluster-randomized trial relates to the choice and definition of the clusters that are to be randomized (unit of randomization) during the course of the trial. Many cluster-randomized trials aim to measure the effectiveness of interventions that are to be implemented by specific institutions or organizations, such as schools, health units or workplaces. Health units that are randomized in cluster-randomized trials include hospitals, clinics, general practices and individual practitioners. The clusters in these trials generally consist of the patients attending these health units. Randomization of health units is most often used to evaluate the effectiveness of new strategies for the diagnosis and management of medical conditions. These often require the training of medical staff in new protocols and approaches, and a common reason for choosing cluster randomization is a concern that contamination may occur if individual patients are randomized

(Hayes et al, 2009). Thus RESASTER trial will use EDs as unit of randomization. Eligibility criteria for this clusters is defined as follows:

2.7.1 Cluster inclusion criteria

- EDs located in teaching and non teaching hospitals across the province of Ontario in Canada (1st and 2nd level of care)
- Accessibility to emergency physician and physician specialists for the assessment of patients with syncope in the emergency department
- Hospital chief of medical staff approval of the protocol
- Hospital administration approval of the protocol
- Hospital ethics board approval of the protocol

2.7.2 Cluster exclusion criteria

- Hospitals with established syncope unit or specialized syncope service
- Pediatric hospitals

2.8 Unit of inference

The unit of inference or analysis in a cluster-randomized trial is defined at the individual level (patients) while randomization is performed at a higher level of subject aggregation (cluster). RESASTER trial will use patients attending to EDs

as the unit of inference. Eligibility criteria for the unit of inference is defined as follows:

2.8.1 Patient Inclusion Criteria

- Patient seeking medical attention for syncope or TLOC in the emergency department
- Age 18 years older

2.8.2 Patient Exclusion Criteria

- Previous investigated and diagnosed cause of syncope or TLOC
- Life expectancy less than one year according to the underlying diseases prognosis
- Past medical history of cognitive impairment
- Past medical history of psychotic impairment
- Active drug/alcohol intoxication at the time of ED presentation

2.9 Participant Recruitment

Study participants will be recruited at the different EDs across the province of Ontario in Canada, when a triage clinical diagnosis of syncope or TLOC is made on registration at admission to hospital. This will be reported by the triage

registered nurse (RN) to the ED physicians or specialists who will record the patients name and the basic demographic data in a pre-printed form and will apply the RESASTER-SCP or will continue with the standard syncope diagnosis approach depending on the cluster randomization. The health care provider has the responsibility to assess the eligibility and ethical considerations of the individual patient. Patient contact and clinical information will be recorded in the electronic database and forward to research personnel who will follow the patient outcomes and will report to the investigators, adjudicator committee and the cluster representation mechanism group (See section 6.2 for details). The study principal investigators will not be involved in recruiting the study participants. However, when required they will provide assistance to the most responsible physician in direct charge of participant care when there is a difficult clinical assessment that required expert clarification such as inclusion and exclusion criteria, withdraw from the study, ethical issues, etc.

If larger units such as hospital, schools, worksites or cities are to be randomized, it is useful to begin with a census of eligible clusters to assess participant recruitment feasibility. This will help to determine whether or not there are enough clusters to achieve the desired power as well as to establish the generalizability of the study results. Key-decision makers for each cluster need to

be identified and then approached to determine their level of interest in participating in the trial (Donner et al, 2000).

As mentioned before, syncope is a common presenting symptom in the general population accounting to 1 to 1.5% of emergency department (ED) annual visits as well as 6% of hospital admissions in North America (ACEP, 2001; Huff et al, 2007). Moreover, recent studies found a remarkably constant frequency of syncope in community-based EDs in Europe, with an incidence of >1% of all attendances (range 0.9–1.7%) (Moya et al, 2009). Similarly Thiruganasambandamoorthy et al (Thiruganasambandamoorthy et al, 2010) reported that in just one urban tertiary center in Canada (Ottawa Hospital Civic Campus ED) staffed by certified emergency physicians and with 60.000 annual patient visits the number of patients presenting with syncope were about 564 during an 18 months period (0.6%). Sixteen academic teaching hospitals and 46 non-teaching general hospitals with more than 100 beds across the province (Ontario_Ministry_of_Health_and_Long_Term_Care, 2011) can potentially be used as unit of randomization. This number of potential clusters will be enough to conduct the trial in the province of Ontario achieving pre-specified power of the study. Using the Ottawa experience and assuming that only 50% (31) of the total

62 hospitals agreed to participated in RESASTER, I estimate a potential of 17,000 individual participants (272 per cluster).

2.10 Randomization procedures

The main reasons for adopting randomization include: impartiality of allocation, transparency for replication, balance of confounding factors, blinding and formal justification for the use of statistical inference (Hayes et al, 2009). All these reasons apply also to cluster randomized trials. However, many cluster-randomized trials include a relatively small number of clusters and this mean that adequate balance may not be achieved by the use of simple unrestricted randomization. This is one of the main reasons for considering the use of matched or stratified study designs that represent special types of restricted randomization that are explained in detail below.

2.10.1 Restricted randomization

Matches and stratified designs are examples of restricted randomization since these schemes involve selecting randomly from a smaller set of allocations fulfilling certain restrictions. Stratified designs impose fewer constraints, so the allocations are chosen from a larger subset of the total number possible under unrestricted randomization. However these designs can often not be relied upon

to achieve adequate balance, particularly where there are several variables on which balance is required. Fortunately, there is an alternative approach to achieving overall balance between the interventions arms, which does not require identifying subgroups of clusters that are matched on all of the balancing variables. This approach uses a combination of stratification and restriction. The stratification can improve efficiency by allowing comparisons to be made within relatively homogenous strata while additional restriction criteria can be used to ensure overall balance. This may be done restricting to allocations that satisfy certain pre-determined criteria. One allocation is then selected randomly from this restricted subset (Hayes et al, 2009).

In RESASTER study a restricted randomization approach will be applied stratifying by the type of hospital used as cluster: teaching and non-teaching hospital. This balancing by logistical reasons is important since the nature of practice in teaching and non-teaching hospitals can vary. The first one involves a more complex interdisciplinary approach between emergency physician, specialists and subspecialists involving also medical students and postgraduate trainees. In non teaching hospitals usually there is a more individual approach of practice based on staffing capabilities. This sequence generation based on stratification is imposed to minimize imbalance across interventions groups. It is

important to acknowledge that any constraint imposed on the cluster randomized trial affects the sample size and the analysis and thus should be reported (Campbell et al, 2004).

Having decided to use restricted randomization for a particular trial, there three general types of balance criteria that may be chosen (Hayes et al, 2009): Balance on covariates, balance on sample size and balance for political or logistical reasons. Having defined a proposed list of balance criteria, balance for logistical reasons in the case of RESASTER, a computer program designed by the Population Health Research Institute (PHRI) information technology department will be used to test each possible allocation against these criteria, and to determine how many allocations will be acceptable. If this number is too small, or renders impossible some configurations that would best be allowed, the balance criteria;/ may need to be relaxed in order for the restricted randomization to have a greater validity of statistical inference.

2.10.2 Allocation concealment

In cluster-randomized trials, it is established that the allocations of subjects to interventions arms should be in general concealed until the point at which they have been enrolled to the trial. A substantial bias is associated with

inadequate concealment of allocation. Advanced knowledge of the intervention arm to which potential cluster would be allocated may consciously or unconsciously influence the decision of the researcher or cluster representatives as to whether the cluster should be included in the trial. The procedures to obtain consent for clusters should seek the agreement that the cluster can be enrolled in the trial on the basis that interventions will be randomly allocated (Hayes et al, 2009).

After the stratified sequence generation is applied, Hospitals agreeing to participate in the RESASTER study will be electronically assigned to RESASTER-SCP intervention or usual care using simple random allocation. This will be supported by computer software specifically designed by PHRI, the coordinating institution of RESASTER affiliated to McMaster University. Thus the allocation of intervention is predetermined for each member of the clusters. Hence the potential for selection bias (selective inclusion of patients into the trial) within clusters is particularly high. It is therefore important to outline any strategies that will be implemented to minimize the possibility of selection bias according to the CONSORT statement (Campbell et al, 2004). In RESASTER study investigators will report whether all the patients within the cluster are

included or not using the local computerized medical record software or the patient chart hard copy provided by the different health records services.

2.10.3 Validity of Restricted Randomization

A completely cluster randomised trial design is said to be valid if every pair of clusters has the same probability of being allocated to the same intervention. Failure to satisfy this condition may result in correlations between the clusters in each intervention arm. Estimated variances, used to carry our significance test and derive confidence intervals, are generally based on the assumption of independence between each arm. An invalid design may therefore result in tests with incorrect Type I error, and confidence intervals with incorrect coverage (Hayes et al, 2009). Thus, when using restricted randomization, researchers therefore need to assess the validity of the chosen randomization scheme. At a minimum, this should involve checking the number of acceptable allocations. If the number of unrestricted allocations is large, but the number after restrictions is very small (< 100), it is quite likely that there will be serious departures from the conditions of validity. In this case it is necessary to relax the balance criteria to obtain an acceptable number of allocations. Also, it is necessary to check on how many pairs of clusters are assigned together to the same treatment arm.

Chapter 3 Measurements and Data Collection Considerations

3.1 Introduction

This chapter addresses the selection of instruments for measuring outcomes in the RESASTER Study and issues related to data collection. Considerations when selecting measurement instruments will include the definition of syncope (section 3.2), primary outcome (section 3.3) and secondary outcomes (section 3.4) descriptions. Moreover, the procedures for outcomes follow-up (section 3.5) and data collection (section 3.6) will be also described in this chapter.

3.2 Syncope definition in RESASTER Study

Syncope will be defined as a TLOC due to transient global cerebral hypoperfusion characterized by rapid onset, short duration, and spontaneous complete recovery. For recruitment and inclusion of patients in RESASTER Study the syncope definition from the ESC will be adopted (Moya et al, 2009).

3.3 Primary Outcome

In cluster randomized trials statistically significant differences in a pre-defined primary outcome would have more weight than an isolated statistically significant differences from multiple outcomes (Hayes et al, 2009).

RESASTER study will use *necessary admission to hospital* in patients presented to the ED with syncope / TLOC as primary outcome at individual level in the context of a specific intervention (RESASTER-SCP vs. usual care) at the cluster level (EDs). Participants that required immediate admission to hospital are defined at high risk of adverse outcomes including sudden cardiac death (malignant arrhythmia leading to cardiac arrest with or without successful resuscitation) and life threatening conditions (e.g. active bleeding, severe infection, respiratory distress) that can require intensive care.

An independent expert adjudicator committee will confirm the primary and secondary outcomes after a detailed review of the participant chart and data collection forms, taking into account the different clinical findings and investigation results of the study participant. The adjudicator committee will be blind in regards to the cluster intervention allocation. It would be integrated by two experts in the area of syncope in the province of Ontario and will not include any

of the principal investigators. In cases of disagreement, a third syncope expert will adjudicate the outcome.

3.4 Secondary Outcomes

The list of serious outcomes was as defined in the San Francisco Syncope Rule study (Quinn et al, 2004) and included any of the following: death, myocardial infarction, arrhythmia, pulmonary embolism, stroke, subarachnoid hemorrhage, any significant bleeding, any procedural intervention to treat a related cause of syncope, any condition causing or likely to cause a return emergency visit, or hospitalization for a related event within 30 days. RESASTER study will use the definitions as per the original study, and they are given below:

a) Death: Death from any cause. Confirmation of death within 30 days was done by review of records in all local hospitals and records from the provincial coroner's office.

b) Myocardial infarction: Defined as an increase in troponin level or ECG changes consistent with ischemia/infarction and with an accompanying diagnosis of myocardial infarction. It must have been confirmed in the patients chart by the emergency physician or the most responsible physician.

c) Arrhythmia: Defined as any rhythm abnormality (previously known or new) captured on monitoring and thought to have a temporal relationship to the symptom or that required treatment.

d) Pulmonary embolism: Diagnosis made by ventilation-perfusion scan, computed tomography (CT) scan of the chest or pulmonary angiography. If pulmonary embolism was of mild or moderate probability as per the ventilation-perfusion scan and the patient received or was considered for treatment, then we will classify the case as a pulmonary embolism.

e) Stroke: Defined by presence of a persistent neurologic deficit with symptoms temporally related to the syncope episode.

f) Subarachnoid hemorrhage: Confirmed by CT/magnetic resonance imaging of the brain, with or without spinal fluid analysis by lumbar puncture.

g) Significant hemorrhage: Defined as a detected source of bleeding requiring transfusion.

h) Any procedural intervention to treat a related cause of syncope: Any patients who underwent an acute intervention that would have caused them to

return if they had been discharged will be considered to have had a serious outcome. Monitoring of patients, medication changes, or rehydration will not be considered to be an acute intervention.

i) Any condition causing or likely to cause a return emergency visit: Patients with return visits related to the initial syncope visit and who are subsequently admitted or experienced any of the above outcomes will be considered to have had an adverse outcome. If the return visit is related but they are discharged without any acute intervention, they will be classified as not having experienced an adverse outcome.

j) Hospitalization for a related event within 30 days: Defined as hospitalization for syncope or any other related symptom within 30 days of the initial visit.

k) Syncope diagnosis including: Reflex syncope (also known as neurocardiogenic, vasovagal, situational syncope), autonomic dysfunction (orthostatic intolerance), cardiac syncope (ACS, arrhythmia, valvular disease and cardiomyopathy), pulmonary embolism, stroke, subarachnoid hemorrhage, other significant hemorrhage and syncope NYD (unknown etiology)

3.5 Outcomes follow-up

Because it would be difficult to arrange follow-up within 7 days with a specialist or family physician, a 1, 3, 6 and 12 months outcomes follow up will be arranged). ED, outpatient clinics and inpatient medical records from all local cluster participants will be reviewed by adjudicator committee for occurrence of outcomes within 1, 3, 6 and 12 months of recruitment and inclusion in the study. Death records will be also reviewed from all participating institutions and the provincial coroner's office in order to accurately register the primary cause of death. Moreover since there is a possibility that a patient is admitted to a non-participant cluster or another participant hospital, a RESASTER assistant will contact the patient telephonically at 1, 3, 6 and 12 months in order to determine wheatear or not out of protocol visits to ED have occurred. Overall, data will be collected for both the occurrence and place of occurrence of serious adverse outcomes (i.e. in the ED, the hospital or at place of residence).

3.6 Data collection

The physicians involved in the study-participant care will enter and record the relevant clinical information on an Internet-secure data collection form (see appendix 3). This information will be securely stored in a password-protected

server located at the Population Health Research Institute (PHRI) affiliated to McMaster University, the coordinating institution of the RESASTER study. A research assistant and statistician will review periodically the database in order to solve queries and enter missing information accessing patient medical records. Overall, Internet access is available in all the major Hospital across Canada guarantying the data collection and storage. Off line secure intranet data acquisition software will be available in every cluster for backup in case no Internet connection is accessible at the time of the study participant recruitment and assessment. Moreover, a hard copy data collection form will be available as back up in case no computer connection is available. Finally, physicians will be instructed in data entering and recording during practical workshops offered by RESASTER principal investigators before the start of the study in the different clusters.

Chapter 4 Statistical Considerations

4.1 Introduction

In this chapter, I discuss the issues pertaining to statistical methods of analysis. This chapter includes a description of Intracluster correlation coefficient (section 4.2) sample size calculation (section 4.3) and analytical methods (section 4.4).

4.2 Intracluster correlation coefficient

In brief, the primary implication of adopting a cluster-randomized design is that outcomes in individuals within the same cluster tend to be correlated. The statistical measure of the degree of correlation is known as the intracluster correlation coefficient (ICC) and is defined as the proportion of variation in the outcome that can be explained by the variation between clusters. As standard sample size calculations and analysis techniques assume that outcomes for individuals are independent (that is, uncorrelated), more sophisticated approaches have to be adopted to account for the clustering in the data. For a completely randomized cluster trial, standard sample size estimates need to be

inflated by a factor 1 + (n - 1) ρ, where n is the cluster size and ρ is the ICC, to appropriately account for the clustering in the data (Campbell et al, 2005).

This, the intracluster correlation coefficient (ICC) or ρ (the Greek rho), is a measure of the relatedness of clustered data. It accounts for the relatedness of clustered data by comparing the variance within clusters with the variance between clusters (Killip et al, 2004). Mathematically, it is the between-cluster variability divided by the sum of the within-cluster and between-cluster variabilities (see figure 2).

Equation 1. Intracluster Correlation Coefficient

$$\text{ICC or } \rho = \frac{s_b^2}{\left(s_b^2 + s_w^2\right)},$$

Where S_b^2 = the variance between clusters, and S_w^2 = the variance within clusters. Values of ρ range from 0 to 1 in human studies. From equation 1, as the within-cluster variance (s_w^2) moves toward 0, ρ gets closer and closer to 1. In the theoretical case where ρ = 1, all responses within a cluster are identical. In that case the effective sample size is reduced to the number of clusters. A very small value for ρ implies that the within-cluster variance is much greater than the between-cluster variance, and a ρ of 0 shows that there is no correlation of

responses within a cluster. Usually, values of ρ are between 0.01 and 0.02 in human studies. The calculation of ρ usually requires a pilot study. It is encouraged that all investigators to publish their ρ values, which will (eventually) aid in being able to estimate ρ for a given type of population (Killip et al, 2004).

4.3 Sample size calculation

A quantitative justified sample size calculation is almost universally regarded as a fundamental design feature of a properly controlled clinical trial (Donner et al, 2000). Trials that are too small have low power, meaning that there is an unacceptably high probability of obtaining a non-significant result even when an intervention actually has a medically important effect. Even if a significant result is obtained, the confidence interval on the effect estimate is likely to be wide, indicating a failure to quantify the effect accurately. Conversely, the value of a negative result is compromised, since the wide confidence interval means that the trial is unable to distinguish between an intervention with no effect and one with a substantial beneficial or adverse effect (Hayes et al, 2009).

There are a number of issues common to sample size calculation that apply to any randomized trial in general (Donner et al, 2000). These include: (1) identification of the primary study outcome, (2) determination of the minimal

clinical important difference (MCID) and (3) specification of a statistical test or confidence interval method along with its directionality. An overall useful rule of thumb is to regard four clusters per arm as an absolute minimum (Hayes et al, 2009)

To retain equivalent power to an individually randomized trial, the number of individuals in a cluster randomized trial needs to be increased. The key determinants of this increase are the intracluster correlation coefficient (see section 4.2) and the cluster size. Reports of cluster-randomized trials should state the assumptions used when calculating the number of clusters and the cluster sample size (Campbell et al, 2004)

In accounting for the similarities among clustered subjects, there is a net loss of independent data. The *effective sample size* (ESS) is the term used to describe the sample size in clustered samples compared with the number of subjects actually enrolled in the study. For example, if you have 4 physicians' offices enrolling 32 patients each, you have 128 subjects in your study. Depending on the intracluster correlation coefficient and the design effect, however, you may effectively have far fewer subjects enrolled in your trial from a statistical perspective. To get the effective sample size, the total sample size (the number of patients per cluster times the number of clusters) is divided by a

correction factor that includes ρ and the sample size per cluster (m). This correction factor is called the design effect (DE). In the case study above, we created the special case of clustered data with all groups having the same number of subjects (each physician recruited 32 patients). In this special case (see equations 3 and 4)

Equation 2. Effective Sample Size

$$\text{ESS} = \frac{\text{mk}}{\text{DE}}$$

Equation 3. Design Effect

$$DE = 1 + \rho\,(m - 1),$$

Where m = number of subjects in a cluster, k = number of clusters, mk = total number of subjects in a clustered study, ESS = effective sample size, DE = design effect, and ρ = intracluster correlation coefficient (see equation 1). If $\rho = 0$, then the design effect = 1, and the sample size is unaffected. If $\rho > 0$, even if it is still very small, the design effect may be magnified by a large cluster size (m). This would then reduce the effective sample size of the study (see equation 2). If $\rho = 1$, the DE (see equation 3) is more than 1, and the effective sample size

therefore reduces to k, the number of clusters. These equations can be reversed in the planning phase to calculate correctly the total sample size needed for a clustered study. All power calculations and resultant sample size estimates can be calculated initially using usual formulas for a clustered study, which will give researchers the effective sample size. Equation 2 can be used to find *mk*, or the total required sample size, given the effective sample size and design effect adjustment (Killip et al, 2004).

Since RESASTER study main objective is to compare proportions of individuals with the outcome of interest (necessary admission to hospital) in the intervention and control group a standard formula for sample size calculation for proportions has been used to calculated the sample size (see Equation 4):

Equation 4. Sample size formula

$$n = (z_{\alpha/2} + z_{\beta})^2[\pi_0(1 - \pi_0) + \pi_1(1 - \pi_1)]/(\pi_0 - \pi_1)^2$$

Where, π_1 and π_0 are the true (population) proportions in the presence or absence of the intervention, respectively and π_0 - π_1 is the MCID (Hayes et al, 1999). The sample size will be adjusted using DE, in order to determine the ESS in the 62 clusters.

RESASTER sample size calculation took into account the ICC, the number of events in the intervention and control group, the expected effect (MCID), and the power of the study. The value of *m* has been set as 274 (see section 2.9). A pre-specified of 80% power has been set as well as an α level of 0.05. Since there are no previous published studies to calculate the ICC as well as there are no randomized control trials reporting MCID, a table with different ICCs and MCID has been designed to select an arbitrary sample size of 600 participants (ICC = 0.02 and MCID = 15%) per treatment arm. A pilot study is needed to better understand the feasibility of the RESASTER sample size and potentially re-calculate the ICC and MCID according to preliminary results. Table 4.1 presents sample sizes according to different ICC and MCID.

		MCID			
ICC		**10%**	**15%**	**20%**	**25%**
	0.01	950	346	147	61
	0.02	1645	600	255	106
	0.03	2340	853	363	151
	0.04	3035	1107	471	195
	0.05	3731	1360	579	240

Table 4.1 Sample Size according to ICC and MCID

4.4 Analytical methods

A wide range of analytical methods has been proposed for the analysis of cluster-randomized trials. There are two main approaches to analysis, based on cluster-level summaries or individual level data. In cluster randomized trials the cluster constitutes the experimental unit. Observations may be done at different levels and there may therefore be several different types of observational unit. In the simplest case, observations may be made only on the individual subjects in each cluster. More often, however, data will also be collected on cluster-level variables and, in some cluster randomized trials, there may be also intermediate levels of observation (Hayes et al, 2009).

To ensure that the parameter of interest is clearly specified, it is usually helpful to write down the proposed statistical model. In the case of a cluster-randomized trial, this model needs to take account of between-cluster variability. The terms of this model can then be used to specify the parameters of interest. The appropriate statistical model depends on the type of endpoint, and one can consider event rates, proportions and means in turn (Hayes et al, 2009).

4.4.1 Cluster-level analysis

This approach is a conceptually very simple two-stage process. First, a summary measure is obtained for each cluster, and this is usually based on data collected on the endpoint of interest among individuals in that cluster. Thus, the total experience of the individuals in the trial is reduced to 2c numbers, if there are c cluster in each of two study arms. At a second stage, these two sets of cluster specific measures are compared using an appropriate statistical method. The most common approach is to use a simple two-sample *t*-test. Sometimes a logarithmic transformation is required when there is a skewed distribution. Thus, the *t* distribution can be used both to carry out a significance test of the null hypothesis of no intervention effect, and to obtain a confidence interval for the parameter of interest. The *t*-test has been shown to be highly robust to departures from the underlying assumptions. Occasionally a more conservative option is the use of nonparametric methods using Wilcoxon's rank sum test or permutation test. Allowance can be made for covariates by carrying out an individual-level regression at the first stage of analysis, ignoring the clustering of the data. All variables of interest are entered into a regression model except for the intervention effect. Then, the summary measure for each cluster is the residual based on comparison of the observed outcome in that cluster and the predicted outcome in the absence of an intervention effect. If there is truly an intervention effect, then the residuals will differ systematically between the two

intervention arms, and comparison of the residuals at the second stage, using the *t*-test or other methods, provides measures of the intervention effect that are adjusted for the covariates considered in the first stage (Hayes et al, 2009). A common objection to *cluster-level* analysis is that information is wasted when the data are reduced to a set of two summary measures. Investigators note that, in a trial with 10 clusters per arm but following many thousands of individuals, the final analysis is based on two columns of 10 numbers. However, the power and precision of the study will depend on the observed variability in the outcome between clusters. The observed between-cluster variance will be reduced if a large number of individuals are studied in each cluster.

4.4.2 Individual-level analysis

While the cluster-level approach to analysis is robust, it may not be statistically the most efficient approach, especially when the clusters are of widely varying size since the cluster summaries measures are not identically distributed and have different variance. A greater power and precision would potentially be achieved if the analyses are weighted to take into account the different variances carrying out regression analysis based on the individual level in a one stage process. It is essential that the regression method chosen take proper account of between cluster variations. The most common choices of regression model are

those based on random effects models, including: Poisson regression for event rates, logistic regression for proportions and linear mixed models for quantitative outcomes. An important advantage of individual-level regression methods over the simpler two-stages methods is that the effects of modelled covariates are estimated and presented simultaneously with the intervention effects (Hayes et al, 2009).

In summary, it is recommended to use of the two-stage method for the analysis of cluster-randomized trials with fewer than 15-20 clusters per treatment arm. That would be with the case of RESASTER Study since there is an estimated sample size of 600 individuals per intervention arm and potentially 274 participants per cluster for an approximately 3 to 4 clusters per arm required. For larger number of clusters, either approach can be used, but individual level regression is likely to be more efficient, especially if cluster size vary substantially (Hayes et al, 2009).

4.4.3 Proposed statistical analysis

4.4.3.1 Statistical tests to be conducted

Estimates of intervention effects may be obtained using means, overall rates and proportions computed from all individuals in the cluster. These are

equivalent to the standard ratio estimates obtained from cluster sampling theory. The use of this approach is most appropriate if the chosen clusters are randomly selected from a well-defined study population of interest, in the case of RESASTER study, individuals presenting to the ED with syncope. Primary and secondary outcomes variables in RESASTER study are binary endpoints where the objective is to compare proportions of subjects with specific characteristics in the intervention and control arms. Example would include the prevalence of some condition at end of follow-up (e.g. myocardial infarction, pulmonary embolism etc), or the cumulative incidence or risk of some outcome during a specified follow-up period (Hayes et al, 2009). The specific statistical methods that will be used for analysing each of the outcomes variables are presented in Table 4.2:

Outcome	Type	Statistical Test
Necessary admission to hospital (primary)	Proportion	Z-test
Death from any cause	Proportion	Z-test
Myocardial infarction	Proportion	Z-test
Arrhythmia	Proportion	Z-test
Pulmonary embolism	Proportion	Z-test
Stroke	Proportion	Z-test
Subarachnoid hemorrhage	Proportion	Z-test
Significant hemorrhage	Proportion	Z-test
Any procedural intervention to	Proportion	Z-test

treat a reacted cause of syncope		
Any condition causing or likely to cause a return to the ED	Proportion	Z-test
Hospitalization for a related event within 30 days	Proportion	Z-test
Syncope diagnosis	Proportion	Z-test

Table 4.2 Outcome's Method of Analysis

Moreover outcomes measurements will be adjusted for possible effects of clustering by using a variance-inflation factor based on the average cluster size and intracluster correlation (Donner et al, 1986).

4.4.3.2 Intention to treat analysis

All participants in RESASTER study will be retained within the trial after allocation whether or not they fit the inclusion criteria and even if they could not or did not receive the allocated treatment (This is the principle of intention to treat analysis) (Puffer et al, 2003). The intention to treat approach has two main purposes. Firstly, the approach maintains treatment groups that are similar apart from random variation. This is the reason for randomization, and the feature may be lost if analysis is not performed on the groups produced by the randomization process. Secondly, intention to treat analysis allows for non-compliance and deviations from policy by clinicians (Hollis et al, 1999). The main problem in the

application of the intention to treat approach is the handling of missing data. Inappropriate handling of missing responses can produce misleading conclusions. The strategies to handle missing data are discussed in section 5.7.

4.4.3.3 Subgroup analysis

In RESASTER study a subgroup analysis at the cluster level will be performed using the type of hospital (teaching vs. non-teaching) as a variable of characterization. In addition a subgroup analysis at the individual level will be performed according to age (<40 and >40 years old), gender and etiology of syncope. Differences in effect between subgroups should be interpreted with caution. Significance tests for interaction (effect modification) will be carried out to assess whether these differences could easily have occurred by chance (Hayes et al, 2009)

4.4.3.4 Adjustment for multiple testing

The Bonferroni Correction will be used in RESASTER study in order to adjust for multiple testing. Bonferroni adjustments are based on the following reasoning (Bland et al, 1995): If a null hypothesis is true (for instance, two treatment groups in a randomised trial do not differ in terms of cure rates), a significant difference ($P<0.05$) will be observed by chance once in 20 trials. This

is the type I error, or α. When 20 independent tests are performed (for example, study groups are compared with regard to 20 unrelated variables) and the null hypothesis holds for all 20 comparisons, the chance of at least one test being significant is no longer 0.05, but 0.64. The formula for the error rate across the study is $1-(1-\alpha)^n$, where n is the number of tests performed. However, the Bonferroni adjustment deflates the α applied to each, so the study-wide error rate remains at 0.05. The adjusted significance level is $1-(1-\alpha)^{1/n}$ (in this case 0.00256), often approximated by α/n (in this case 0.0025). The main weakness is that the interpretation of a finding depends on the number of other tests performed and the likelihood of type II errors is also increased, so that truly important differences are deemed non-significant (Perneger, 1998).

4.4.3.5 Study results reporting

Overall, the results of RESASTER study will be reported following the CONSORT statement guidelines for reporting cluster randomized trials (Campbell et al, 2004). This will include the clusters and individual participants flow through each stage (a diagram will be used). Specifically, for each group RESASTER investigators will report the numbers of clusters and participants randomly assigned, receiving intended treatment, completing the study protocol, and analysed for the primary outcome. Also a description of protocol deviations from

study as planned, will be presented with reasons why these changes where made. Moreover, recruitment data will be reported including dates defining the periods of recruitment and follow up. Baseline information for each group for the individual and cluster levels as applicable will be reported as well. Furthermore, the number of clusters and participants (denominator) in each group included in each analysis will be presented. The results will be reported in absolute numbers when feasible (eg 10/20 not 50%). For each primary and secondary outcome, a summary of results for each group for the individual or cluster level as applicable, and the estimated effect size and its precision (e.g. 95% confidence interval) and a coefficient of intracluster correlation (ICC or k) for each primary outcome will be reported. P values will be reported for each variable. Ancillary analyses will be also reported including subgroup analyses and adjusted analyses, indicating those pre-specified and those exploratory. Results will be based on intention to treat analysis as described above. An explicitly description will be given regarding the handling of deviations from randomised allocation and missing data.

Chapter 5 Potential design challenges and study limitations

5.1 Introduction

In this chapter, I discuss potential challenges and limitations that RESASTER may face. The chapter includes potential issues with threats to internal and external validity (section 5.2 and 5.3) minimizing commission and omission errors (section 5.4), pilot study (section 5.5), losses of follow-up (section 5.6), strategies for achieving desired power (section 5.7), missing data handling (section 5.8) and sensitivity analysis (section 5.9).

5.2 Threats to Internal Validity

Internal validity refers to the extent to which differences identified between randomized groups are a result of the intervention being tested. It thus depends on good design, conduct, and analysis of the trial, with minimal bias. In addition, without a sufficient sample size, differences that do exist between randomized groups that are a result of the intervention being tested might not be detected; sufficient sample size can also be considered a marker of internal validity (Eldridge et al, 2008). For cluster randomized trials, statisticians have repeatedly emphasized the importance of accounting for the clustered nature of the data in

sample size calculations and analysis but investigators have not always heeded this guidance (Eldridge et al, 2008).

A potential barrier to internal validity in RESASTER is the lack of concealment of allocation of those identifying or recruiting individuals into a cluster-randomized trial. As discussed above, in cluster randomized trials there are two levels of participant: the cluster and the individual. Identification or recruitment of individuals, or both, often takes place after randomization (of clusters) and if those carrying out the identification or recruitment of patients at this post-randomization stage are not blinded to allocation status, bias can occur (Eldridge et al, 2008). Puffer and colleagues recommend that the study report include a clear statement about when individual participants are identified and whether or not those recruiting are blind to allocation status (Puffer et al, 2003). RESASTER study will record in detail the recruitment process including restriction and allocation concealment status. Generally, the physician in a specific cluster will not be blinded in regards to intervention allocation status. Moreover, the Lack of blinding of the outcome assessment is usually considered the most serious potential source of bias (Schulz et al, 2002). This inability to blind health professionals (and sometimes individual participants) is a distinctive disadvantage of cluster-randomized trials (Eldridge et al, 2008). However, in most of the cluster randomized trials it is possible to assess outcomes in blinded

fashion. In the case of RESASTER study, since there is not gold standard to assess the outcomes, the adjudicator committee will be blind in regards to the cluster intervention allocation.

5.3 Threats to External Validity

External validity refers to the extent to which study results can be applied to other individuals or settings. Several frameworks have been developed that are helpful in assessing this. The RE-AIM framework was developed by Glasgow and colleagues to characterize the public health impact of interventions (Glasgow et al, 1999) and has been used to assess the external validity of evaluations of interventions common in cluster randomized trials. Four features of RE-AIM are related to external validity: reach, adoption, implementation, and maintenance (see Table 5.1 The RE-AIM framework).

To judge adoption (the extent to which the settings included in the study are representative of a wider population of settings and adequately described), a reader needs information on eligibility criteria for clusters, numbers of clusters randomized and analyzed, and a discussion of generalizability of trial findings to clusters as well as individuals, all factors recommended in the extension to the CONSORT statement for cluster randomized trials (Campbell et al, 2004). Cluster

recruitment rate also contributes to an assessment of adoption. The implementation of an intervention as intended requires the cooperation of the clusters in potentially two distinct ways. Firstly, health professionals in clusters must comply with any intervention targeted at them—for example, the RESASTER-SCP. Secondly, they must deliver components of the intervention they are supposed to be actively involved in—for example, extra counseling sessions to patients (Eldridge et al, 2008).

Dimension	Definition
Reach	Extent to which patients included in evaluation are representative of the population of interest and adequately described
Efficacy	Success rate of intervention if it is implemented as in guidelines
Adoption	Extent of which study settings are representative of wider population of settings and are adequately described
Implementation	Extent to which intervention is implemented as intended in real world. This includes acceptability (adherence to any intervention components targeted directly at health professionals in clusters) and feasibility (extent to which health professional deliver the intervention)
Maintenance	Extent to which programme is sustained over time

Table 5.1 The RE-AIM framework (Eldridge et al, 2008)

Overall, the results of RESASTER should be generalizable to ED (unit of randomization) across Ontario and subsequently to Canada, regardless of their affiliations with a university (Faculty of health sciences or school of medicine) (academic centres and regional hospitals respectively). Moreover, the study results, application of RESASTER-SCP, will be generalizable to patients presenting to the emergency department with syncope (unit of inference).

5.4 Minimizing commission and omission errors

Wu et al (Wu et al, 1997) defined error as a commission or an omission with potentially negative consequences for the patient that would have been judged wrong by skilled and knowledgeable peers at the time it occurred, independent of whether there were any negative outcomes. This definition excludes the natural history of the disease that does not respond to treatment and the foreseeable complications of a correctly performed procedure, as well as cases in which there is reasonable disagreement over whether a mistake occurred. Thus, an error of omission is a failure of action such as a missed diagnosis, a delayed evaluation, failure to admit to hospital or a failure to prescribe needed drug treatment (Weingart et al, 2000). Conversely an error of commission is an incorrect action, usually not indicated, such as administering

the wrong drug to the wrong patient at the wrong time or admitting a patient to hospital when admission is not needed (Weingart et al, 2000)

In RESASTER study, minimizing omission and commission errors, defined as failure to admit a high-risk patient and admitting a low risk patient to hospital respectively, is a key factor to guaranteeing that the study provides an unbiased answer to the question. To minimize these errors when RESASTER-SCP is applied in each specific cluster a few steps will be taken as follows:

- A failure mode effect analysis (FMEA) will be applied to identify, anticipate, and remedy steps in the RESASTER-SCP implementation that are likely to lead to errors of omission and commission (Benjamin, 2003). FMEA has been used for many years in other industries such as aviation. It has recently been adapted to problems encountered in health care. The steps in conduction a FMEA include: selecting the process to analyze (RESASTER-SCP), assemble a multidisciplinary team (RESASTER investigators), identify all the steps in the process that could fail (Patient eligibility, clinical stability and RESASTER-SCP individual application), diagram the process to be assessed, assess the risk priority, likelihood and severity of the error, redesign the process if is necessary and identify ways to measure and track performance (RESASTER steering committee).

- Emergency medicine and specialist physicians in the RESASTER intervention cluster will be educated and trained by study investigators before starting the recruitment, in regards to RESASTER-SCP bedside implementation. This will be done through interactive lectures; specific reading material, local visits and interning based training.

- A computerized tool for the application of the RESASTER-SCP will be used in order to systematically evaluate the patient eligibility, clinical stability and criteria for admission to hospital.

5.5 Pilot study

Pilot studies for phase III trials - which are comparative randomized trials designed to provide preliminary evidence on the clinical efficacy of a drug or an intervention - are routinely performed in many clinical areas. Also commonly known as "feasibility" studies, they are designed to assess critical issues that may affect the overall main study design (Thabane et al, 2010). In general, the rationale for a pilot study can be grouped under several broad classifications – process, resources, management and scientific (Thabane et al, 2010):

- *Process:* This assesses the feasibility of the steps that need to take place as part of the main study. Examples include determining recruitment rates, retention rates, etc.
- *Resources:* This deals with assessing time and budget problems that can occur during the main study. The idea is to collect some pilot data on such things as the length of time to mail or fill out all the survey forms.
- *Management:* This covers potential human and data optimization problems such as personnel and data management issues at participating centers.
- *Scientific:* This deals with the assessment of treatment safety, determination of dose levels and response, and estimation of treatment effect and its variance.

In general, sample size calculations may not be required for some pilot studies. It is important that the sample for a pilot be representative of the target study population. It should also be based on the same inclusion/exclusion criteria as the main study. As a rule of thumb, a pilot study should be large enough to provide useful information about the aspects that are being assessed for feasibility. The sample used in the pilot may be included in the main study, but caution is needed to ensure the key features of the main study are preserved in the pilot (e.g. blinding in randomized controlled trials). Thabane et al (Thabane et

al, 2010) recommend if any pooling of pilot and main study data is considered, this should be planned beforehand, described clearly in the protocol with clear discussion of the statistical consequences and methods. The goal is to avoid or minimize the potential bias that may occur due to multiple testing issues or any other opportunistic actions by investigators. In general, pooling when done appropriately can increase the efficiency of the main study.

It is always important to state the criteria for success of a pilot study. The criteria should be based on the primary feasibility objectives. These provide the basis for interpreting the results of the pilot study and determining whether it is feasible to proceed to the main study. In general, the outcome of a pilot study can be one of the following: (1) Stop - main study not feasible; (2) Continue, but modify protocol - feasible with modifications; (3) Continue without modifications, but monitor closely - feasible with close monitoring and (4) Continue without modifications - feasible as is (Thabane et al, 2010).

There is one important ethical aspect about pilot studies that has received little or no attention from researchers, research ethics boards and ethicists alike. This pertains to the issue of the obligation that researchers have to patients or participants in a trial to disclose the feasibility nature of pilot studies. This is essential given that some pilot studies may not lead to further studies. Canadian researchers are also encouraged to follow the Tri-Council Policy Statement

(TCPS) (Tri-Council_Policy_Statement, 2005). That too does not address how pilot studies need to be approached. It seems to us that given the special nature of feasibility or pilot studies, the disclosure of their purpose to study participants requires special wording - that informs them of the definition of a pilot study, the feasibility objectives of the study, and also clearly defines the criteria for success of feasibility (Thabane et al, 2010).

In summary, pilot studies are designed to assess the safety of treatment or interventions; to assess recruitment potential; to assess the feasibility of international collaboration or coordination for multicenter trials; and to increase clinical experience with the study medication or intervention for the phase III trials. They are the best way to assess feasibility of a large, expensive full-scale study, and in fact are an almost essential pre-requisite. Conducting a pilot prior to the main study can enhance the likelihood of success of the main study and potentially help to avoid doomed main studies (Thabane et al, 2010).

5.6 Issues involving losses to follow-up

The possibility of loss to follow-up is potentially serious in all randomized trials, but can be particularly severe problem in cluster-randomized trials having a relatively long follow-up time. For trials in which the interventions are applied at

the cluster level, with little or no attention given to individual study participants, the overall attrition rate may well exceed this. Thus, some investigators have deliberately adapted an oversampling strategy to help compensate for such losses, followed by aggressive follow-up of those subjects leaving their cluster (Donner et al, 2000).

Aside from the risk of loss to follow up associated with individual subjects, cluster randomized trials must also deal with the possibility that the entire clusters may drop out. For example, if there are problems with labour relations at a particular work site, all workers at that site may be lost to follow-up. Randomizing more clusters than are formally required to detect a specific intervention effect also allows for the inevitable uncertainty associated with the prior assessment of parameters needed for the application of the sample size formulas, formulas that in any given should be treated as approximate. On the other hand, sometimes a reassigning of the clusters is needed after randomization for reasons of cost, feasibility or politics and the clusters do not received the assigned intervention. Thus, the analysis is not always done by "intention to treat" since the primary analysis does not include all the clusters. Formulas are available that can be used to adjust sample size estimates under fairly simple models of non-adherence. However, there is clearly no substitute for taking all possible steps to

enhance, monitor and verify compliance with the trial protocol on the part of all study participants (Donner et al, 2000).

5.7 Achieving desired power

Even carefully designed trials may be underpowered. The are a number of strategies that can be applied to RESASTER study in order to reduce this possibility (Donner et al, 2000):

- In general, subjects and clusters that agree to participate in clinical trials and cluster randomized trials respectively are rarely representative of the general population impairing external validity. On the other hand, "investigator driven" selection effects in the form of restrictive eligibility criteria can sometimes have a positive impact on trial power and hence on internal validity. This can be accomplished by placing geographic or other relevant restrictions on the clusters to be randomized, thus reducing between cluster variability (Teaching vs. non-teaching hospital)

- Since the time and expense needed to obtain large amounts of data from study participants might reduce subject compliance and the subsequent

retention rates of both clusters and subjects within clusters. Therefore, all data that will be collected in RESASTER has been carefully justified.

- Realistic estimates of the MCID are required if trials are to be adequately powered. Similar considerations apply to estimating the likely loss to follow-up rate. In RESASTER, a reserve of clusters will be created to be available for randomization in the event that this became necessary to preserve the pre-specified level of power.

5.8 Missing data handling

Various imputation methods may be used to estimate the missing data. However, clinical trials usually do not collect sufficient data to allow good estimation, and the only commonly feasible options are using the last observed response (carry forward) or assuming that all missing responses were constant. Extreme case analysis (for example, all patients lost to the group that fared better are assigned a poor outcome; all lost to the group that fared worse are assigned a good outcome) has also been recommended but this is unlikely to yield a conclusive answer in practice. More sophisticated techniques for handling missing data are available but depend on assumptions about the missing data mechanism which cannot be completely verified in most clinical trials. In general,

multiple imputations are used to produce a conservative estimate of treatment effect. However, no imputation method can give an unbiased estimate of the treatment effect unless the assumptions made about the missing data are valid. To fully appreciate the potential influence of missing responses, some form of sensitivity analysis is recommended, examining the effect of different strategies on the conclusions (Hollis et al, 1999). Thus RESASTER study will use multiple imputations to handling the missing data in the basis of intention to treat analysis.

5.9 Sensitivity analysis

Sensitivity analysis is the study of how the variation (uncertainty) in the output of a statistical model can be attributed to different variations in the inputs of the model (Saltelli, 2008). In other words, it is a technique for systematically changing variables in a model to determine the effects of such changes.

Sensitivity analyses are conducted by estimating the required trial sample size under a number of different scenarios. Investigator are often surprised to learn from such analysis that even small changes in the expected effect of intervention, in the number of subjects sampled per cluster or in the ICC can have large effects on the required sample size. It may be argued that sensitivity analysis serve a particularly important role in the planning of cluster randomized

trials. This is largely a consequence of the difficulty investigators may have in obtaining accurate estimates of either between-cluster variability or ICC. Together with cluster size, these quantities are used to adjust sample size for the variance inflation due to clustering. However, inaccuracies may still remain because estimates of ICC obtained from studies with only small number of cluster are very imprecise (Donner et al, 2000). In RESASTER study a sensitivity analysis for the primary outcome will be conducted to assess robustness of the intervention effects.

Regression to adjust for potential baseline imbalance between groups

Chapter 6 Ethical and Legal Issues

The purpose of this chapter is to address issues related to the conduct of the RESASTER cluster randomized control trial, including funding sources and potential conflict of interest (section 6.1), ethical issues (section 6.2), Health Canada approval and trial registration (section 6.3), participant recruitment (section 6.4), risk and benefits to potential participants (section 6.5) and protection of participant confidentiality (section 6.5).

6.1 Source of Funding and Potential Conflicts of Interest

This study protocol will be submitted to Canadian health research founding agencies for peer review competition. Those include the Canadian Institute of Health Research (CIHR), the Heart and Stroke Foundation of Canada (HSFC) and the Canadian Network and Centre for Trials Internationally (CANNeCTIN). None of the investigators for this study function as employees, officers and directors of those mentioned agencies. Dr. Thabane and Dr. Morillo are advisors and peer reviewers for CIHR, but would declare a potential conflict of interest and would not be present for peer deliberations on the submitted grant.

6.2 Ethical issues in cluster randomized trials

In cluster randomized controlled trials, informed consent for trial entry (that is, for randomization) cannot be obtained individually because one person's choice might impinge and influence on another's (Edwards et al, 1999). This arise some ethical issues due to the unconventional nature of the cluster design. There are two widely used arguments for randomisation by cluster. Firstly, the intervention itself may be administered to and affect entire clusters of people as opposed to individuals within that cluster. Secondly, although the intervention or treatment is given to individuals, it may also affect others within that cluster. This may be because it "leaks," contaminating those who are not supposed to receive it, thereby weakening any estimate of treatment difference (Edwards et al, 1999).

The Canadian Tri-Council Policy Statement (Tri-Council_Policy_Statement, 2005) was designed to protect the welfare and liberty interests of individual research subjects, but little guidance is provided with respect to community-based cluster trials research, let alone cluster randomized trials (Taljaard et al, 2009). The sole exception is the UK Medical Research Council document (Medical_Research_Council, 2002). The council considered that agreement to participation in the trial would normally be necessary from one or a series of ***gatekeepers/guardians***. Since the unit of randomization in RESASTER is the emergency departments, the gatekeepers will normally be the

physician or physicians involved in patient's care). However, neither research ethics committee approval nor gatekeeper agreement is truly equivalent to consent. An individual, body, or mechanism that can represent the interests of the cluster will be established in all centres participating in the study. This will be labelled as the "cluster representation mechanism" (CRM). In RESASTER the CRM will be formed by the chief of staff of the participant ED and a representative of the hospital administration. The ethical principle here is that the CRM must act in good faith, and in this regard only in the interests of the cluster represented CRM, or gatekeepers, may be appropriate advocates or patients who wish to withdraw from the cluster by seeking assignment to another health care team or hospital. The CRM should be independent of the research team to avoid conflicts of interest. Where these cannot be avoided, they must be declared to investigator, the research founding agency, the research ethics committee, and, where possible, to the cluster individual participants (Medical_Research_Council, 2002).

Ethical approval will be obtained from the Research Ethics Board of Hamilton Health Sciences/McMaster University and the different participating institutions across Canada before starting study recruitment. An age limit no less than 18 years is specified because the primary purpose of the study is to focus in

the adult population presenting with syncope to the ED that required either early (admission to hospital) or delayed diagnostic assessment (discharge home with - further follow-up as an outpatient).

Investigators, emergency physicians and specialists are hired through McMaster University and Hamilton Health Sciences and other participant institutions which it will provide insurance in the event of injury sustained while assessing and treating the study participants in the ED. Moreover all physicians in Ontario have individual malpractice insurance through the Canadian Medical Association.

6.3 Health Canada Approval and trial registration

As the study does not involve a new off-label use of a drug or medical device, a Clinical Trial application or a medical Device Licence Application with Health Canada is not required. The study does not involve the use of infectious agents, biosafety hazard, or genetic testing or long-term storage of tissues or bio-samples. However, the study will be registered on the website CLINICALTRIALS.GOV (www.clinicaltrials.gov) that currently contains approximately 9,000 clinical studies sponsored by the National Institutes of Health (United States of America), other federal agencies, Canadian Research

Agencies (e.g. CIHR), international agencies and the private industry. Studies listed in the database are conducted primarily in the United States of America and Canada, but include locations in about 90 countries around the world.

6.4 Risk and Benefits of the Proposed Research to Participants

Participants will benefit from the study since the RESASTER-SCP application will allow the physician to determine if patients can be discharged home from ED, avoiding unnecessary admission to hospital that may impact patient's quality of life and also preventing the occurrence of adverse outcomes in participants that require admission and would not have been admitted in the first instance by the ED physician. Moreover the CRM and the principal investigators will review on a regular basis (every 2 months) the participant's records in order to guarantee that patient care and the diagnostic process is conducted in a proper way. In case of detecting a medical issue this will be reported immediately to primary health care providers for proper intervention and correction. This will be applicable to both study arms (intervention and control clusters).

On the other hand, since RESASTER compares usual care (control cluster) vs. a structured care pathway (intervention cluster) based on previously validated decisions rules, patients will face a small risk of harm due to the actual

intervention. In the absence of a perfect sensitivity and specificity , given the low hospitalization rate in Canada, the study may increase hospitalization rates which potential can lead to side effects such as deep venous thrombosis, pulmonary embolism, nosocomial pneumonia, urinary track infection, C-Difficile infection and delirium.

Moreover, the study does not involve a new off-label use of a drug or medical device that may cause side effect and adverse events to the study participants.

6.5 Protection of participant's information confidentiality

As mentioned before, data collected by physicians and research nurse including participant's demographic information as well as outcomes measurements will be secure in a password-protected server located at the Population Health Research Institute (PHRI) affiliated to McMaster University. Access only will be granted research assistants, investigators, CRM and statisticians for review and analysis.

Chapter 7 Future Directions and Conclusions

7.1 Future Directions

The Results of RESASTER study should provide important information regarding the usefulness of instituting structured care pathways in the assessment of patients presenting with syncope to the ED, since a significant proportion of patients (10%) suffer adverse outcomes after being discharged. This may improve patient safety and will also guide the ED physician and other specialist to a rapid disposition of patients, specially the ones at high risk of adverse events. Moreover, the cost of the syncope assessment may be reduced, saving substantial amount of money to the health care system. Different decision rules and risk stratification scores have been proposed but they have not been systematically compared with the conventional approach in a prospective cluster randomized control trial.

Recently, the CCS published a position paper for standardized approaches to the investigation of syncope (Sheldon et al, 2011). The panel of experts referred that algorithmic testing coupled with implementation tools improves diagnostic yield and reduce costs to the healthcare system. Key tactics to consider in implementation of these strategies would include rapid access to

specialist assessment and provision of an on-line prompting tool for the diagnosis of syncope in the ED.

Future directions aim to develop standardized diagnostic testing pathways and electronic tools that may improve efficiency and reduce unnecessary testing and admission to hospital in patients presenting with syncope / TLOC to the ED.

Moreover, the establishment of formal syncope investigation units in general hospitals across Canada may improve patient care and outcomes. Further studies are needed to evaluate the impact of Syncope Units in patient outcomes and healthcare expending.

7.2 Conclusions

This thesis described some of the methodological issues concerning the design of a cluster randomized trial aiming to determine whether the RESASTER-SCP is superior to usual care in identifying patients at low risk for serious outcomes presenting to the ED with syncope who can be safely discharged home. Thus the aim of a structured care pathway for syncope diagnosis in the ED is: (1) give the patient continuity of care, (2) reduce inappropriate hospitalizations, and (3) set standards of clinical excellence in the field.

Appendix A. The San Francisco Syncope Rule (SFSR)

1. At the time of triage does the patient have a systolic blood pressure less than 90 mmHg?

   Yes: ☐ Admit to hospital (HIGH RISK) No: ☐ Continue to next question

2. Does the patient complain of shortness of breath?

   Yes: ☐ Admit to hospital (HIGH RISK) No: ☐ Continue to next question

3. Does the patient have history of congestive heart failure

   Yes: ☐ Admit to hospital (HIGH RISK) No: ☐ Continue to next question

4. Does the patient have a rhythm on the ECG that is not sinus?

   Yes: ☐ Admit to hospital (HIGH RISK) No: ☐ Continue to next question

5. Does the patient have new changes on their ECG?

   Yes: ☐ Admit to hospital (HIGH RISK) No: ☐ Continue to next question

6. Does the patient have a hematocrit less than 30

Yes: ☐ Admit to hospital (HIGH RISK) No: ☐ Discharge home (LOW RISK)

Definitions

- Triage systolic BP < 90 mmHg: Defined as systolic BP less than 90 mmHg measured by ED nurse triaging the patient.

- History of shortness of breath: Defined as patient suffering from shortness of breath at any time during the visit either that was reported by the patient or elicit by medical personnel.

- History of congestive heart failure: Defined as present or past history of congestive heart failure and reported by the patient or elicit by the medical personnel.

- Abnormal ECG: Defined as any non-sinus rhythm, which could be identified on the 12 lead ECG or during cardiac monitoring in the ED; or any new morphologic changes compared to a prior ECG (if no prior existed, then any new changes are considered to be significant).

- Hematocrit <30: Defined as hematocrit <0.300 as SI units used in Canada.

Appendix B. The OESIL Risk Score

1. Age > 65 years ☐

2. Cardiovascular disease in clinical history ☐

3. Syncope without prodromes ☐

4. Abnormal electrocardiogram ☐

Mortality risk: 0=0%, 1=0.08%, 2=19.6%, 3=34.7% and 4=57.1%.

If OESIL >1: ☐ Admit to hospital (HIGH RISK)

<1: ☐ Discharge home (LOW RISK)

Appendix C. Data Collection Forms

1. **Demographics**
    a. Age (years)
    b. Gender (male / female)
    c. Date of emergency visit (d/m/y)
    d. Physician (code)
    e. Site (Emergency Department)
    f. Physician status (full-time, part-time, resident)
    g. Physician specialty (Emergency Medicine, Internal Medicine, Cardiology, Neurology, Endocrinology, Respirology and Nephrology)
    h. Arrival by ambulance and paramedic findings –
        i. First EMS systolic and diastolic blood pressures
        ii. Amount of fluids given
        iii. Any abnormality (non-sinus rhythm or arrhythmia) detected on EMS rhythm strip/cardiac monitor associated with symptoms or any cause for syncope found by paramedics;
    i. Transfer from another emergency department, if yes, specific reason why patient was transferred
2. **History of Present Illness**

a. Prodromal symptoms:
    i. Light-headedness or dizziness
    ii. Nausea
    iii. Vomiting
    iv. Abdominal pain
    v. Sweating
    vi. Shortness of breath
    vii. If yes duration of symptoms specify (best possible estimate) in seconds or minutes
b. After event or at any time – symptoms
    i. Palpitations
    ii. Chest pain
    iii. Shortness of breath
    iv. Headache
    v. Dizziness
    vi. Numbness
    vii. Focal deficit
    viii. Abdominal pain
c. Exertion prior to syncope (exercise, climbing stairs)
d. Symptoms or heart failure

i. Dyspnea on excertion

ii. Paroxysmal nocturnal dyspnea

iii. Orthopnea

iv. Peripheral edema

e. History of bleeding from any source

3. Past Medical History

a. Arrhythmias (specify atrial/ventricular)

b. Anti-arrhythmic medications (excludes alpha, beta and calcium channel blockers)

c. Congestive Heart Failure

d. Structural heart disease

i. Coronary artery disease

ii. Valvular heart disease

iii. Non ischemic myocardial heart disease

e. Hypertension

f. Diabetes

g. Cerebrovascular accident / Transient ischemic attack

h. Peripheral arterial disease

4. Personal or Family history

a. Congenital heart disease

b. Cardiomyopathy

c. Ventricular dysplasia

d. Prolonged QT

e. Brugada syndrome or family history of sudden deaths

f. Past syncopal episodes

5. Physical Examination

a. Triage vital signs

i. Pulse rate

ii. Blood pressure (systolic and diastolic)

iii. Respiratory rate

iv. Oxygen saturation

b. Postural systolic and diastolic blood pressure readings at the time of physician assessment

i. Supine

ii. Sitting

iii. Standing

iv. Did the patient experience any syncope or pre-syncope symptoms on sitting or standing?

v. Lowest systolic and diastolic blood pressures recorded;

c. Examination findings

i. Murmur

ii. Rales or crackles

iii. Rhonchi or wheeze

iv. Decreased air entry;

v. Is the patient in congestive heart failure?

6. Investigations

a. Laboratory values

i. Lowest values of hemoglobin and hematocrit,

ii. Worst values of sodium and potassium

iii. Worst value of potassium

iv. Highest values of urea, creatinine, creatine kinase and troponin

b. ECG on admission to hospital

i. Heart Rate

ii. Emergency physician's and cardiologist's interpretation of ECG parameters:

1. Rhythm (Sinus or Nonsinus)
2. Premature ventricular beats
3. Premature atrial beats
4. Presence of atrioventricular block and type

5. Presence of right bundle branch or left bundle branch or fasicular blocks
6. Left or right ventricular hypertrophy
7. Left axis deviation
8. Old myocardial infarction
9. ST segment and T wave changes consistent with ischemia or that are secondary (due to ventricular hypertrophy, old infarction or medications) or that are non-specific,repolarization abnormalities
10. QRS duration
11. QT interval
12. Delta waves
13. Rright bundle branch pattern with ST-elevation in leads V1-V3 (Brugada syndrome)
14. Pattern of negative T waves in V1-V3 with epsilon waves (Arrhythmogenic right ventricular dysplasia)

c. Cardiac monitor

   i. Duration of monitoring

   ii. Any abnormality (non-sinus rhythm or arrhythmia) detected on cardiac monitoring and were symptoms associated with it

d. Carotid sinus massage results if done

e. CT head results for new and clinically important abnormalities

7. Usefulness, comfort about the intervention (RESASTER-SCP arm) and physician judgment

a. How useful was the RESASTER-SCP in deciding disposition on this patient? (very useful, useful, not useful)

b. How comfortable are using the RESASTER-SCP? (comfortable, uncomfortable or very comfortable)

8. Disposition

a. Specialty to which patient was referred - to whom

i. Cardiology

ii. Internal medicine

iii. Neurology

iv. Others

b. Timing of the referral

c. Was the patient admitted to hospital?

d. Was the patient referred for outpatient investigations?

i. 24 hour Holter monitoring

ii. Echocardiogram

iii. Eelectroencephalogram (EEG)

iv. or others

9. Final diagnosis in the Emergency Department

a. Reflex syncope (Also known as neurocardiogenic, vasovagal or situational syncope)
b. Autonomic dysfunction (Orthostatic intolerance)
c. Cardiac syncope (ACS, arrhythmia, valvular disease and cardiomyopathy)
d. Pulmonary embolism
e. Stroke
f. Subarachnoid hemorrhage
g. Other significant hemorrhage
h. Syncope NYD (unknown etiology)

Bibliography

ACEP. *Clinical Policy: Critical Issues in the Evaluation and Management of Patients Presenting with Syncope*. Ann Emerg Med 2001; 37:771-6.

Benjamin DM. *Reducing Medication Errors and Increasing Patient Safety: Case Studies in Clinical Pharmacology*. Journal of clinical pharmacology 2003; 43:768-83.

Birnbaum A, Esses D, Bijur P, Wollowitz A, Gallagher EJ. *Failure to Validate the San Francisco Syncope Rule in an Independent Emergency Department Population*. Ann Emerg Med 2008; 52:151-9.

Bland JMandAltman DG. *Multiple Significance Tests: The Bonferroni Method*. BMJ 1995; 310:170.

Brignole M, Alboni P, Benditt D, Bergfeldt L, Blanc JJ, Bloch Thomsen PE, van Dijk JG, Fitzpatrick A, Hohnloser S, Janousek J, Kapoor W, Kenny RA, Kulakowski P, Moya A, Raviele A, Sutton R, Theodorakis G, Wieling W. *Guidelines on Management (Diagnosis and Treatment) of Syncope*. Eur Heart J 2001; 22:1256-306.

Brignole M, Alboni P, Benditt DG, Bergfeldt L, Blanc JJ, Bloch Thomsen PE, van Dijk JG, Fitzpatrick A, Hohnloser S, Janousek J, Kapoor W, Kenny RA, Kulakowski P, Masotti G, Moya A, Raviele A, Sutton R, Theodorakis G, Ungar A, Wieling W. *Guidelines on Management (Diagnosis and Treatment) of Syncope--Update 2004*. Europace 2004a; 6:467-537.

Brignole M, Alboni P, Benditt DG, Bergfeldt L, Blanc JJ, Thomsen PE, Gert van Dijk J, Fitzpatrick A, Hohnloser S, Janousek J, Kapoor W, Kenny RA, Kulakowski P, Masotti G, Moya A, Raviele A, Sutton R, Theodorakis G,

Ungar A, Wieling W, Priori SG, Garcia MA, Budaj A, Cowie M, Deckers J, Burgos EF, Lekakis J, Lindhal B, Mazzotta G, Morais J, Oto A, Smiseth O, Menozzi C, Ector H, Vardas P. *Guidelines on Management (Diagnosis and Treatment) of Syncope-Update 2004. Executive Summary*. Eur Heart J 2004b; 25:2054-72.

Brignole M, Ungar A, Bartoletti A, Ponassi I, Lagi A, Mussi C, Ribani MA, Tava G, Disertori M, Quartieri F, Alboni P, Raviele A, Ammirati F, Scivales A, De Santo T. *Standardized-Care Pathway Vs. Usual Management of Syncope Patients Presenting as Emergencies at General Hospitals*. Europace 2006; 8:644-50.

Campbell MK, Elbourne DR, Altman DG. *Consort Statement: Extension to Cluster Randomised Trials*. BMJ 2004; 328:702-8.

Campbell MK, Fayers PM, Grimshaw JM. *Determinants of the Intracluster Correlation Coefficient in Cluster Randomized Trials: The Case of Implementation Research*. Clinical trials 2005; 2:99-107.

Colivicchi F, Ammirati F, Melina D, Guido V, Imperoli G, Santini M. *Development and Prospective Validation of a Risk Stratification System for Patients with Syncope in the Emergency Department: The Oesil Risk Score*. Eur Heart J 2003; 24:811-9.

Cosgriff TM, Kelly AM, Kerr D. *External Validation of the San Francisco Syncope Rule in the Australian Context*. CJEM 2007; 9:157-61.

Del Rosso A, Ungar A, Maggi R, Giada F, Petix NR, De Santo T, Menozzi C, Brignole M. *Clinical Predictors of Cardiac Syncope at Initial Evaluation in Patients Referred Urgently to a General Hospital: The Egsys Score*. Heart 2008; 94:1620-6.

Donner AandWells G. *A Comparison of Confidence Interval Methods for the Intraclass Correlation Coefficient*. Biometrics 1986; 42:401-12.

Donner AandKlar N. *Design and Analysis of Cluster Randomization Trials in Health Research*. London
New York, N.Y.: Arnold ;
Co-published by the Oxford University Press, 2000.

Edwards SJ, Braunholtz DA, Lilford RJ, Stevens AJ. *Ethical Issues in the Design and Conduct of Cluster Randomised Controlled Trials*. BMJ 1999; 318:1407-9.

Eldridge S, Ashby D, Bennett C, Wakelin M, Feder G. *Internal and External Validity of Cluster Randomised Trials: Systematic Review of Recent Trials*. BMJ 2008; 336:876-80.

Epstein AE, DiMarco JP, Ellenbogen KA, Estes NA, 3rd, Freedman RA, Gettes LS, Gillinov AM, Gregoratos G, Hammill SC, Hayes DL, Hlatky MA, Newby LK, Page RL, Schoenfeld MH, Silka MJ, Stevenson LW, Sweeney MO, Smith SC, Jr., Jacobs AK, Adams CD, Anderson JL, Buller CE, Creager MA, Ettinger SM, Faxon DP, Halperin JL, Hiratzka LF, Hunt SA, Krumholz HM, Kushner FG, Lytle BW, Nishimura RA, Ornato JP, Riegel B, Tarkington LG, Yancy CW. *Acc/Aha/Hrs 2008 Guidelines for Device-Based Therapy of Cardiac Rhythm Abnormalities: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the Acc/Aha/Naspe 2002 Guideline Update for Implantation of Cardiac Pacemakers and Antiarrhythmia Devices): Developed in Collaboration with the American Association for Thoracic Surgery and Society of Thoracic Surgeons*. Circulation 2008; 117:e350-408.

Fayers PM, Jordhoy MS, Kaasa S. *Cluster-Randomized Trials*. Palliat Med 2002; 16:69-70.

Ganzeboom KS, Mairuhu G, Reitsma JB, Linzer M, Wieling W, van Dijk N. *Lifetime Cumulative Incidence of Syncope in the General Population: A Study of 549 Dutch Subjects Aged 35-60 Years*. J Cardiovasc Electrophysiol 2006; 17:1172-6.

Gibbons CHandFreeman R. *Delayed Orthostatic Hypotension: A Frequent Cause of Orthostatic Intolerance*. Neurology 2006; 67:28-32.

Glasgow RE, Vogt TM, Boles SM. *Evaluating the Public Health Impact of Health Promotion Interventions: The Re-Aim Framework*. American journal of public health 1999; 89:1322-7.

Goldberger JJ, Cain ME, Hohnloser SH, Kadish AH, Knight BP, Lauer MS, Maron BJ, Page RL, Passman RS, Siscovick D, Stevenson WG, Zipes DP. *American Heart Association/American College of Cardiology Foundation/Heart Rhythm Society Scientific Statement on Noninvasive Risk Stratification Techniques for Identifying Patients at Risk for Sudden Cardiac Death: A Scientific Statement from the American Heart Association Council on Clinical Cardiology Committee on Electrocardiography and Arrhythmias and Council on Epidemiology and Prevention*. Circulation 2008; 118:1497-1518.

Guyatt GH, Oxman AD, Vist GE, Kunz R, Falck-Ytter Y, Alonso-Coello P, Schunemann HJ. *Grade: An Emerging Consensus on Rating Quality of Evidence and Strength of Recommendations*. BMJ 2008; 336:924-6.

Hayes RJandBennett S. *Simple Sample Size Calculation for Cluster-Randomized Trials*. International journal of epidemiology 1999; 28:319-26.

Hayes RJandMoulton LH. *Cluster Randomised Trials*. 1 Boca Raton: CRC Press, 2009.

Hollis SandCampbell F. *What Is Meant by Intention to Treat Analysis? Survey of Published Randomised Controlled Trials*. BMJ 1999; 319:670-4.

Huff JS, Decker WW, Quinn JV, Perron AD, Napoli AM, Peeters S, Jagoda AS. *Clinical Policy: Critical Issues in the Evaluation and Management of Adult Patients Presenting to the Emergency Department with Syncope*. Ann Emerg Med 2007; 49:431-44.

Kapoor WN, Karpf M, Wieand S, Peterson JR, Levey GS. *A Prospective Evaluation and Follow-up of Patients with Syncope*. N Engl J Med 1983; 309:197-204.

Kapoor WNandHanusa BH. *Is Syncope a Risk Factor for Poor Outcomes? Comparison of Patients with and without Syncope*. Am J Med 1996; 100:646-55.

Killip S, Mahfoud Z, Pearce K. *What Is an Intracluster Correlation Coefficient? Crucial Concepts for Primary Care Researchers*. Annals of family medicine 2004; 2:204-8.

Martin TP, Hanusa BH, Kapoor WN. *Risk Stratification of Patients with Syncope*. Ann Emerg Med 1997; 29:459-66.

McDermott DandQuinn J. *Response to "Failure to Validate the San Francisco Syncope Rule in an Independent Emergency Department Population"*. Ann Emerg Med 2009; 53:693; author reply 693-4.

Medical_Research_Council. *Cluster Randomized Control Trials: Methodological and Ethical Considerations*. 2002; 9-11.

Middlekauff HR, Stevenson WG, Stevenson LW, Saxon LA. *Syncope in Advanced Heart Failure: High Risk of Sudden Death Regardless of Origin of Syncope*. J Am Coll Cardiol 1993; 21:110-6.

Moya A. *The European Society of Cardiology Guidelines for the Diagnosis and Management of Syncope Reviewed by Angel Moya, Md, Fesc, Chair of the Guideline Taskforce with J. Taylor, Mphil*. Eur Heart J 2009; 30:2539-40.

Moya A, Sutton R, Ammirati F, Blanc JJ, Brignole M, Dahm JB, Deharo JC, Gajek J, Gjesdal K, Krahn A, Massin M, Pepi M, Pezawas T, Granell RR, Sarasin F, Ungar A, van Dijk JG, Walma EP, Wieling W, Abe H, Benditt DG, Decker WW, Grubb BP, Kaufmann H, Morillo C, Olshansky B, Parry SW, Sheldon R, Shen WK, Vahanian A, Auricchio A, Bax J, Ceconi C, Dean V, Filippatos G, Funck-Brentano C, Hobbs R, Kearney P, McDonagh T, McGregor K, Popescu BA, Reiner Z, Sechtem U, Sirnes PA, Tendera M, Vardas P, Widimsky P, Acarturk E, Andreotti F, Asteggiano R, Bauersfeld U, Bellou A, Benetos A, Brandt J, Chung MK, Cortelli P, Da Costa A, Extramiana F, Ferro J, Gorenek B, Hedman A, Hirsch R, Kaliska G, Kenny RA, Kjeldsen KP, Lampert R, Molgard H, Paju R, Puodziukynas A, Raviele A, Roman P, Scherer M, Schondorf R, Sicari R, Vanbrabant P, Wolpert C, Zamorano JL. *Guidelines for the Diagnosis and Management of Syncope (Version 2009): The Task Force for the Diagnosis and Management of Syncope of the European Society of Cardiology (Esc)*. Eur Heart J 2009; 30:2631-71.

Ontario_Ministry_of_Health_and_Long_Term_Care. *Classification of Hospitals*. http://www.health.gov.on.ca/english/public/contact/hosp/hospcode.html - groups 2011;

Perneger TV. *What's Wrong with Bonferroni Adjustments*. BMJ 1998; 316:1236-8.

Puffer S, Torgerson D, Watson J. *Evidence for Risk of Bias in Cluster Randomised Trials: Review of Recent Trials Published in Three General Medical Journals*. BMJ 2003; 327:785-9.

Quinn J, McDermott D, Stiell I, Kohn M, Wells G. *Prospective Validation of the San Francisco Syncope Rule to Predict Patients with Serious Outcomes*. Ann Emerg Med 2006; 47:448-54.

Quinn JV, Stiell IG, McDermott DA, Sellers KL, Kohn MA, Wells GA. *Derivation of the San Francisco Syncope Rule to Predict Patients with Short-Term Serious Outcomes*. Ann Emerg Med 2004; 43:224-32.

Quinn JV, Stiell IG, McDermott DA, Kohn MA, Wells GA. *The San Francisco Syncope Rule Vs Physician Judgment and Decision Making*. Am J Emerg Med 2005; 23:782-6.

Reed MJ, Newby DE, Coull AJ, Jacques KG, Prescott RJ, Gray AJ. *The Risk Stratification of Syncope in the Emergency Department (Rose) Pilot Study: A Comparison of Existing Syncope Guidelines*. Emerg Med J 2007; 24:270-5.

Reed MJ, Newby DE, Coull AJ, Prescott RJ, Jacques KG, Gray AJ. *The Rose (Risk Stratification of Syncope in the Emergency Department) Study*. J Am Coll Cardiol 2010; 55:713-21.

Reed MJ, Henderson SS, Newby BS, Gray AJ. *One-Year Prognosis after Syncope and the Failure of the Rose Decision Instrument to Predict One-Year Adverse Events*. Annals of emergency medicine 2011;

Saltelli A. *Global Sensitivity Analysis : The Primer*. Chichester, England ; Hoboken, NJ: John Wiley, 2008.

Sarasin FP, Louis-Simonet M, Carballo D, Slama S, Rajeswaran A, Metzger JT, Lovis C, Unger PF, Junod AF. *Prospective Evaluation of Patients with Syncope: A Population-Based Study*. Am J Med 2001; 111:177-84.

Schulz KFandGrimes DA. *Blinding in Randomised Trials: Hiding Who Got What*. Lancet 2002; 359:696-700.

Serrano LA, Hess EP, Bellolio MF, Murad MH, Montori VM, Erwin PJ, Decker WW. *Accuracy and Quality of Clinical Decision Rules for Syncope in the Emergency Department: A Systematic Review and Meta-Analysis*. Annals of emergency medicine 2010; 56:362-373 e1.

Sheldon RS, Morillo CA, Krahn AD, O'Neill B, Thiruganasambandamoorthy V, Parkash R, Talajic M, Tu JV, Seifer C, Johnstone D, Leather R. *Standardized Approaches to the Investigation of Syncope: Canadian Cardiovascular Society Position Paper*. The Canadian journal of cardiology 2011; 27:246-53.

Shen WK, Decker WW, Smars PA, Goyal DG, Walker AE, Hodge DO, Trusty JM, Brekke KM, Jahangir A, Brady PA, Munger TM, Gersh BJ, Hammill SC, Frye RL. *Syncope Evaluation in the Emergency Department Study (Seeds): A Multidisciplinary Approach to Syncope Management*. Circulation 2004; 110:3636-45.

Soteriades ES, Evans JC, Larson MG, Chen MH, Chen L, Benjamin EJ, Levy D. *Incidence and Prognosis of Syncope*. N Engl J Med 2002; 347:878-85.

Sun BC, Emond JA, Camargo CA, Jr. *Direct Medical Costs of Syncope-Related Hospitalizations in the United States*. Am J Cardiol 2005; 95:668-71.

Sun BC, Mangione CM, Merchant G, Weiss T, Shlamovitz GZ, Zargaraff G, Shiraga S, Hoffman JR, Mower WR. *External Validation of the San Francisco Syncope Rule*. Ann Emerg Med 2007; 49:420-7, 427 e1-4.

Taljaard M, Weijer C, Grimshaw JM, Belle Brown J, Binik A, Boruch R, Brehaut JC, Chaudhry SH, Eccles MP, McRae A, Saginur R, Zwarenstein M, Donner A. *Ethical and Policy Issues in Cluster Randomized Trials: Rationale and Design of a Mixed Methods Research Study*. Trials 2009; 10:61.

Thabane L, Ma J, Chu R, Cheng J, Ismaila A, Rios LP, Robson R, Thabane M, Giangregorio L, Goldsmith CH. *A Tutorial on Pilot Studies: The What, Why and How*. BMC medical research methodology 2010; 10:1.

Thiruganasambandamoorthy V, Hess EP, Alreesi A, Perry JJ, Wells GA, Stiell IG. *External Validation of the San Francisco Syncope Rule in the Canadian Setting*. Ann Emerg Med 2010; 55:464-72.

Thiruganasambandamoorthy V SI, Wells GA. *Frequency and Outcomes of Syncope in the Emergency Department*. CJEM 2008; 10:279.

Tri-Council_Policy_Statement. *Ethical Conduct for Research Involving Humans*. http://www.pre.ethics.gc.ca/policy-politique/tcps-eptc/docs/TCPS October 2005_E.pdf 2005;

van Dijk JGandSheldon R. *Is There Any Point to Vasovagal Syncope?* Clin Auton Res 2008; 18:167-9.

van Dijk N, Sprangers MA, Colman N, Boer KR, Wieling W, Linzer M. *Clinical Factors Associated with Quality of Life in Patients with Transient Loss of Consciousness*. J Cardiovasc Electrophysiol 2006; 17:998-1003.

Weingart SN, Wilson RM, Gibberd RW, Harrison B. *Epidemiology of Medical Error*. BMJ 2000; 320:774-7.

Wieling W, Krediet CT, van Dijk N, Linzer M, Tschakovsky ME. *Initial Orthostatic Hypotension: Review of a Forgotten Condition*. Clin Sci (Lond) 2007; 112:157-65.

Wu AW, Cavanaugh TA, McPhee SJ, Lo B, Micco GP. *To Tell the Truth: Ethical and Practical Issues in Disclosing Medical Mistakes to Patients*. Journal of general internal medicine 1997; 12:770-5.