RESEARCH DURING AN EMERGENCY:
A SERIES OF INQUIRIES CONCERNING THE OUTBREAK OF
SEVERE ACUTE RESPIRATORY SYNDROME (SARS) IN TORONTO

By

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For the degree of Doctor of Philosophy
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ABSTRACT

Research During an Emergency: A Series of Inquiries concerning the Outbreak of Severe Acute Respiratory Syndrome (SARS) in Toronto
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Background: Researchers and research ethics boards (REBs) in Toronto were unprepared for the SARS outbreak. There is a paucity of literature about how to review emergency-related protocols during a public emergency and so REBs had no guidance about how to review SARS-related protocols.

Research questions: The thesis presents four related research inquiries based on the following four objectives: 1) to conduct a comprehensive evaluation of the one-year outcomes in SARS survivors; 2) to explore the ethical issues that emerged during the conduct of the SARS outcomes study; 3) to understand the impact of the SARS outbreak on research ethics review (RER) of SARS-related protocols; and 4) to propose a new framework of RER for use during public emergencies.

Methods: Included in this thesis are an observational study, an analytic reflection, a grounded theory study, and a translation of the knowledge gained in the first three parts of the thesis into a framework of RER that is meaningful and actionable.

Results: Part I describes the recovery made by SARS survivors from their acute illness. In part II, I explore ethical issues that arose during the conduct of the study including: social and scientific value and scientific validity of emergency research, and respect for privacy and
confidentially. Part III presents a theory about how researchers, REBs and public health interacted during the outbreak and in part IV, I propose ‘emergency review’ a framework for RER for use during a publicly declared emergency.

**Conclusions:** The natural experiment that was the SARS outbreak in Toronto revealed the vulnerabilities in the structure of REBs. I highlight three conclusions which are the highest priority to provide further development in this field. These are: 1) when REBs, researchers and public health are not effectively communicating during a public emergency, the work of each group is disrupted; 2) institutional conflict of interest occurred during the research ethics review of SARS-related protocols and may be amplified during a public emergency and 3) there is a need for a multi-site review structure that could be activated on short notice to review protocols related to the emergency situation.
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I wish to express my enormous gratitude to all who have made this doctoral journey possible, mostly fun and always a rich learning experience.

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I also acknowledge the extraordinary efforts of the SARS survivors and their caregivers who so generously donated their time to participate in the SARS outcomes study to help educate us about how SARS affected their lives. The ‘Three Solitudes’ study would not have been possible without the willingness of my nineteen interviewees to make time in their
busy schedules to speak with me. Each was very willing to share, often in great detail, the challenges that they faced throughout the SARS outbreak.

I also want to acknowledge the contributions made to this thesis in the early years by Dr. Art Slutsky, Dr. George Tomlinson and Dr. Jim Brunton. They formed part of my committee throughout the years of the SARS outcomes study and helped to guide me through the conduct of the study under the difficult circumstances of the outbreak.

My parents Peter and Jane Tansey instilled in me a love of books and a love of learning as well as providing me with the opportunity to complete my studies as an undergraduate. They were proud when I chose to proceed with higher level studies, but neither survived to the completion of this work. I miss you both.

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List of Abbreviations

AAHRPP - Association for the Accreditation of Human Research Protection Programs
AIDS - Acquired Immunodeficiency Syndrome
ARDS - Acute Respiratory Distress Syndrome
ARECCI - Alberta Research Ethics Community Consensus Initiative
AUCC - Association of Universities and Colleges in Canada
BRANY - Biomedical Research Alliance of New York
CAREB - Canadian Association of Research Ethics Boards
CAS - Caregiver Assistance Scale
CCAC - Canadian Council on Animal Care
CDC - Centers for Disease Control and Prevention
CIHR - Canadian Institutes of Health Research
CIS - Caregiver Impact Scale
CIOMS - Council for International Organizations of Medical Sciences
Co-I - Co-Investigator
COI - Conflict of Interest
CoV - Coronavirus
CSRN - Canadian SARS Research Network
DSMB - Data Safety and Monitoring Board
FDA - Federal Drug Administration
FRSQ - Fonds de la Recherche en Santé du Quebec
FWA - Federalwide Assurance
GCP - Guidelines for Good Clinical Practice
GTA - Greater Toronto Area
HCW - Health Care Workers
HPPA - Health Protection and Promotion Act
HIV - Human Immunodeficiency Virus
ICU - Intensive Care Unit
ID - Infectious Disease
IRB - Institutional Review Board
IT - Information Technology
JCB - Joint Centre for Bioethics, University of Toronto
MAC - Medical Advisory Committee
MACRO - Multicenter Academic Clinical Research Organization
MCS - Mental Component Summary Score
MOU - Memorandum of Understanding
N/A - Not Available
NIH - National Institutes of Health
NSERC - Natural Science and Engineering Research Council of Canada
OCREB - Ontario Cancer Research Ethics Board
OHRP - Office for Human Research Protections
OTS - Ontario Thoracic Society
PI - Principal Investigator
CHAPTER 1: INTRODUCTION TO THE THESIS

A. Purpose of the Thesis

This is a thesis that is at the interface between clinical science and bioethics. It grew out of my own experience as a member of a research team that conducted a study about SARS survivors, just as the SARS outbreak was waning in Toronto. Because of this experience, I focus on the ethical issues that are relevant to research as it was carried out during the public emergency that was the SARS outbreak in Toronto.

The purpose of this thesis is to describe and analyze the outcomes of severe acute respiratory syndrome (SARS) survivors and the ethical issues related to research inquiries conducted during the SARS outbreak. Specifically, this will include an examination of the process of research ethics review and the formulation of a novel framework for research ethics review during a public emergency. To explore these aims, the thesis presents four related research inquiries based on the following four objectives:

1. To conduct a comprehensive and family-centred evaluation of the one-year outcomes in survivors of SARS and their family caregivers (called the SARS outcomes study hereafter);

2. To explore the ethical issues that emerged during the planning and implementation of the SARS outcomes study;

3. To understand the impact of the SARS outbreak on research ethics review of SARS-related protocols;

and

4. To propose a new framework of research ethics review called ‘emergency review’ for use during public emergencies.
The thesis is organized into four parts that align with the above-mentioned aims. I use three distinct methods in a complementary manner as different methodologies help to elucidate different areas of inquiry. I present multiple empirical studies using clinical epidemiological methods in part I, and grounded theory in part III. Part II is a reflective analytic essay and part IV translates insights from the previous inquiries into a procedural framework to guide research ethics boards during emergencies.

**B. Context of the Thesis**

**B1. Epidemics**

Times of epidemics have been likened to times of war. During wars, emergency procedures are often followed and the normal ethical rules of conduct are superseded by rules that promote the common good. It has been argued that during epidemics the norms for the ethical conduct of research should be slightly different from those that are normally observed. Consideration of public benefit becomes more important and concerns about individual privacy and individual rights may diminish somewhat. While each still remains important, it is their relative contribution that may change. The evaluation of what constitutes an appropriate balance between harms to individuals and potential benefits to society requires balancing the harms of an epidemic to the community with the potential benefits of relevant and timely research. This was eloquently stated in 1970 by Hans Jonas:

“But in times of war our society itself supersedes the nice balance of the social contract with an almost absolute precedence of public necessities over individual rights. In this and similar emergencies, the sacrosanctity of the individual is abrogated, and what for all practical purposes amounts to a near-totalitarian, quasi-communist state of affairs is *temporarily* permitted to prevail.”
Jonas also states:

“Extraordinary danger excuses extraordinary means. This covers human experimentation, which we would like to count, as far as possible, among the extraordinary rather that the ordinary means of serving the common good under public auspices.”

It is not by accident that we speak of an ‘arsenal’ of treatments and ‘killer’ viruses. One author says “an infection is an act of violence; it is an invasion, a rape, and the body reacts violently” Epidemics inspire fear. They can swiftly, unexpectedly and dramatically change the context of our daily lives. Smith et al. explore eight different characteristics of infectious diseases that make them particularly frightening. These are 1) high mortality and morbidity; 2) invasiveness; 3) acuity; 4) communicability; 5) treatability and preventability of many contagious illnesses; 6) host susceptibility; 7) community susceptibility; and 8) high socio-economic impact. While many other diseases have several of these components, few have them all. Taken together, they are what make epidemics so frightening and why ethical issues are raised in slightly different ways in the context of communicable diseases. The SARS outbreak was perceived to have all of these features except perhaps treatability which may have heightened the fear even further. In 1996 Dr. David Satcher, who was at that time director of the United States Centers for Disease Control and Prevention (CDC), said:

“We should expect it [another nasty surprise like AIDS and Ebola in the future] and we should prepare for it because of the ability of microorganisms to mutate, adapt, and change to survive, and to become resistant to antibiotics. But especially because they’re always evolving. That means periodically you’re going to have a new virus, a new bacterium that we haven’t seen before. Or we could have a virus that’s been there all along living in a monkey or some other animal, and then, for some reason, it mutates and becomes virulent to human beings.”

These words have never seemed more relevant than in the aftermath of SARS and as
the H1N1 swine influenza pandemic wanes. The generation of knowledge about new
diseases, or diseases that cross the species barrier and their sequelae, is crucial. We need to
plan for the facilitation of generation of new knowledge i.e., research, and research ethics
review of protocols involving human subjects is an important component of the research
process.

**B2. SARS and Other Emerging Infectious Agents**

SARS was a new virus in a long string of emerging and re-emerging pathogens. In the
last 30 years, several dozen previously unknown diseases have been described. These
include: Ebola virus, Legionnaire’s disease, HIV/AIDS (human immunodeficiency virus/
acquired immunodeficiency syndrome), Hepatitis C, Influenza A or avian flu (1997) and most
recently the H1N1 variant of influenza A. While many of these continue to infect relatively
small clusters of people, HIV/AIDS has reached the status of a pandemic, with over 35% of
the population affected in some sub-Saharan areas. As such, many of the special ethical
issues that arise in outbreaks and in outbreak research have been written about in the context
of HIV/AIDS and HIV/AIDS research. New diseases are continuing to emerge, and it is
important that research to understand these diseases and their treatments be carried out in an
ethical manner.

In 2002, the severe acute respiratory syndrome (SARS) virus mutated so that it
became infectious to human beings. The virus “jumped” from the environmental reservoir
likely in October or November of 2002 in China. It quietly continued to infect relatively few
patients until it came to Hong Kong and in February and March of 2003, it spread from
this hub of commerce and transportation and rapidly infected patients in many parts of the world. On the same day in mid-March that the World Health Organization (WHO) issued its global alert, Toronto’s first case was reported to the Public Health department. No other infectious agent in the long history of contagious illnesses has spread so quickly to the far reaches of the globe.

The SARS story progressed rapidly, largely because the mode of transmission meant that many people were infected quickly. Droplet transmission, so-called ‘super-shedders’, and international travel all contributed to the swift dissemination of the disease. The rapidity with which this happened likely fore-shadows the pattern of any new droplet or airborne agent. Since cases accrue more slowly with other modes of transmission, it generally takes a little longer to recognize an outbreak of these other types. It took several years after AIDS emerged in the United States, for researchers to understand enough about the disease and the epidemic to formulate research questions and to begin implementing research proposals. Because communication can now occur almost instantaneously over of the internet, researchers in the SARS outbreak were able to formulate collaborative plans and research was begun within days of the WHO alert. Within weeks of its naming, the SARS associated coronavirus (CoV) was recognized and the mode of transmission identified; shortly thereafter, the viral genome was decoded.

Why does the speed of the outbreak matter in the evaluation of the ethical issues that are raised in an outbreak? When the outbreak is progressing quickly, ethical considerations including the need for informed consent and respect for vulnerable populations may, in fact, be overlooked. It is important that this not happen, as this is, perhaps, when these
deliberations are most needed. Time pressure was pervasive during the SARS outbreak and may have had important and sometimes unintended consequences. REBs felt time pressure, researchers felt time pressure and public health officials felt time pressure. All of these groups were working quickly to do their part, sometimes, as in the case of REBs, with no guidance about how to proceed in these circumstances. With the AIDS epidemic, now pandemic, the time pressure was not felt in quite the same way as it was during the SARS outbreak. Despite this, arguments were made that AIDS was special, and that special rules were necessary, for design of research trials and expedited access to novel therapies. Much was written about the need for ethical AIDS research and we can take some of those lessons and apply them to other newly emerging disease research. We need to consider the unique ethical issues that arise in the context of epidemics, and how existing research ethics guidelines and research ethics norms may or may not address these issues.

B3. My Story and How I Came to Undertake the Thesis

I started my research journey as a quantitative researcher who was interested in conducting the SARS outcomes study. This was a methodology that I was familiar and comfortable with and which answered the question that I and my collaborators had formulated. The SARS outcomes study was designed to understand the long-term natural history of the disease in those who survived. Importantly, the deleterious mental health consequences (despite near complete physical recovery in the majority) of having suffered a contagious and stigmatizing illness both in patients and their caregivers were significant and may be generalizable to other infectious diseases. This study stands as an important
contribution to the literature on its own, but is also important as a starting point for my critical review of the ethical issues encountered in the conduct of research during a public emergency.

Early in the study, an REB administrator said to me, “Oh, it’s a SARS study – it will be processed more quickly than usual”. This comment had a significant impact on me and led me to think about the changes that must be taking place to facilitate research during the outbreak. Once I began to look for these changes, I saw them all around. Particularly striking in my experience with the SARS outcomes study, were the challenges in obtaining contact information for potential participants and in recruiting patients to the study. The public health department had the names and contact information for patients and we had no relationship with this institution. Liaison with busy infectious disease (ID) specialists was time consuming and many hospitals had no lists of SARS patients. At times, I wondered if the study was worthwhile and if we could recruit enough patients to be able to make a significant contribution to the literature – to the knowledge about SARS patients and what they were experiencing as they recovered from this stigmatizing illness.

I suspected that there were deeper ethical issues underlying these logistical challenges and I wanted to explore these further. For example, when we wanted patients’ contact information from other hospitals and from public health officials, concerns about privacy and confidentiality were highlighted in a way that I had not seen before. The challenge of obtaining patient contact information as well as writing a socially and scientifically valid and valuable protocol quickly, obtaining REB approval in a timely fashion, obtaining informed consent under the conditions created by the public emergency and implementing study procedures and their underlying ethical implications were important and are explored in part
II of this thesis. In order to learn more about the ethical issues that are normally encountered in the conduct of research, I took a research ethics course, joined the Joint Centre for Bioethics (JCB) and began reading about these issues. Part II of the thesis grew from these academic endeavours.

I became fascinated with the role and functioning of REBs and what challenges they faced in their day-to-day work and in particular in the context of an epidemic. I had not read anything about how REBs had handled either SARS-related research or research related to other infectious disease epidemics or public emergencies and did not know how local REBs had reacted to the SARS outbreak in Toronto. Therefore, in part III, I turn my analytic lens on two REBs in Toronto that reviewed SARS-related protocols and conducted a file review of all of the SARS-related submissions that occurred in a study that I call ‘Two REBs’. At the end of this study, I had more questions than answers about the reviews that had taken place and I realized that I needed to use another methodology to explore this further. I therefore enrolled in a course about qualitative methods, read about different types of qualitative analysis, and consulted with experts from the JCB. I realized that what I needed to do was to talk to people who had been involved with ethics review of SARS-related protocols and to use an academically rigourous method to analyze these conversations and distill the findings into a usable format. I chose grounded theory as the most appropriate methodology for my research question which focused on understanding the impact of the SARS outbreak on research ethics review of SARS-related protocols. I call this study ‘Three Solitudes’. Part III of the thesis describes both the ‘Two REBs’ and the ‘Three Solitudes’ studies.

My qualitative interviews highlight the problems REBs encounter during an epidemic.
At that time, there was no guidance on how to perform rapid research ethics review and also to ensure adequate depth of review. In part IV of the thesis, I propose to REBs a procedure that I call ‘emergency review’ that a single REB may use to facilitate approval of emergency-related protocols when the next public emergency occurs. It is meaningful and actionable, an approach that is easy to implement in the timelines available, that provides a quick review as required by most emergencies, but that allows reviewers to consider the many potential risks that might occur in a given emergency-related protocol.

C. Significance of the Thesis

This thesis is unusual in that it uses several different methodologies and foci to access different types of information. The outcomes study uses the conventional observational method of clinical epidemiologic studies. It reports upon a comprehensive and family-centered evaluation of the one-year outcomes in survivors of SARS and their family caregivers. In the second part of the thesis, I use a method that is commonly used in bioethics, i.e, analytic reflection. I start with the experience gleaned in the SARS outcomes study, combine this with relevant literature and reflect how my own experience meshes with and complements the reflections that I found in the literature about the conduct of research and research ethics review in the context of a public emergency. Following this, I use grounded theory, a method first used in sociology, to analyze interviews with stakeholders in the research ethic review process as it occurred in Toronto during the SARS outbreak. I develop a theory about the players in this process i.e., REB members, researchers and public health officials, the stressors that were felt by REBs and the nature of the interactions that took place between these players during the outbreak.
Each part of the thesis is an important step in the academic journey that I took. Each inquiry stands on its own, yet when the four parts are taken together they provide a bigger and broader picture of the impact of the outbreak on research and research ethics review in Toronto. The empirical studies are illuminating, and I was able to take some of the lessons from the outcomes study, the ‘Two REBs’ study and the ‘Three Solitudes’ study and translate them into a process called ‘emergency review’ that is practical and usable by REBs during a public emergency.

**D. Organization of the Thesis**

*Chapter 1: Introduction to the Thesis*

This current chapter outlines the main objectives of the thesis and provides some background about SARS. It then describes briefly my research journey as I pursued this thesis. The significance of the thesis is outlined and the organization of the thesis is revealed.

**PART I.: One-year Outcomes and Health Care Utilization in Survivors of Severe Acute Respiratory Syndrome (The SARS Outcomes Study)**

(Chapters 2-7)

Here, I reproduce the published manuscript of the one-year follow up study of SARS survivors in Toronto as it appears in the Archives of Internal Medicine (2007;167:1312-1320). It was during the implementation of this study, that I began to consider the logistical challenges and the ethical consequences that emerged in the conduct of this research during a public emergency.
Part II: Ethical Issues Encountered in the SARS Outcomes Study: An Analytic Reflection

(Chapters 8 -12)

In this part of the thesis, I undertake an analytic reflection about the ethical issues that were encountered as the study team conducted the SARS outcomes study that is described in part I. These include: 1) social and scientific value and scientific validity; 2) resource allocation which includes sections on multi-centre reviews, feasibility & surge capacity, and funding; 3) respect for free and informed consent which includes sections on: the consent process, the consent form, respect for vulnerable populations, overburdening research subjects, and social obligation to participate in research; 4) respect for privacy and confidentiality; and 5) respect for justice and inclusiveness.

Part III: ‘Two REBs’ & ‘Three Solitudes’: An Inquiry into Two REBs in Toronto During the SARS Outbreak

(Chapters 13 - 18)

This part of the thesis describes two studies that I conducted to understand the impact of the SARS outbreak on research ethics review of SARS-related protocols. The first is a file (or chart) review of all SARS-related protocols submitted to and reviewed by two REBs in Toronto during and just after the SARS outbreak. The second is a grounded theory study about the stressors that were felt by these two REBs as the protocols were reviewed (including lack of availability of reviewers, inability to convene a quorum of REB members in a face-to-face meeting, and the infection control measures that were mandated by the
Ministry of Health and Long-Term Care in Ontario), the players who are the stakeholders in this process (REB members, researchers and public health officials) and the interactions between these three groups.


A novel framework called ‘emergency review’ is presented in this part of the thesis. This may be used by research ethics boards when an emergency situation has been officially declared. This proposal combines three types of review that are reported in the literature and in guidance documents: expedited or delegated review, special scrutiny as described by Levine *et al.* and proportionate review as it is outlined in the revised draft 2nd edition of the Canadian Tri-Council Policy Statement.

*Chapter 23 Conclusion of the Thesis*

This is the concluding chapter to the thesis in which I summarize the main contributions of my thesis, discuss the limitations of the study, and presents some conclusions and areas for future work. I highlight the disruptions that occurred as a result of poor communication among REBs, researchers and public health officials. I emphasize that institutional conflict of interest occurred during the research ethics review of SARS-related protocols and may be amplified during a public emergency. As well, I draw attention to the need for a multi-site review structure that could be activated on short notice to review protocols related to the emergency situation.
Part I

ONE-YEAR OUTCOMES AND HEALTH CARE UTILIZATION IN SURVIVORS OF SEVERE ACUTE RESPIRATORY SYNDROME

One-Year Outcomes and Health Care Utilization in Survivors of Severe Acute Respiratory Syndrome

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Arch Intern Med. 2007;167:1312-1320

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CHAPTER 2: INTRODUCTION TO PART I

The aim of this part of the thesis is to report upon the conduct of a comprehensive and family-centred evaluation of the one-year outcomes in survivors of SARS and their family caregivers. (In later chapters this study will be known as the SARS outcomes study).

2.1 Background

The SARS outbreak proceeded very quickly as described in the introduction to the thesis. So too, the research was formulated quickly. The first Toronto SARS patient presented to hospital at the beginning of March 2003. The illness spread from this index case and by the middle of March, it became apparent that this cluster of patients was likely an outbreak of the disease described by the WHO and reported from Hong Kong. In mid-April 2003, The Toronto Acute Respiratory Distress Syndrome (ARDS) Outcomes group, of which I was a part, was approached by a senior researcher to ask if we were interested in conducting a similar outcomes study with SARS survivors. Under the umbrella of a larger research consortium, The Canadian SARS Research Network (CSRN), a research question was posed and a study design was formulated to evaluate the question. The result was the SARS outcomes study. This was quickly submitted to the REBs at several academic hospitals, and by mid-May, at University Health Network (UHN), we had received permission to proceed with the study. Two consent forms (final versions dated July 7th and 8th) were amended from this initial submission and we were given verbal permission to begin enrollment on July 8th. The first research clinic was held on July 11, 2003. There was no time for a pilot project and
recruiting strategies were not clearly defined or operationalized. Over the course of the next year, REB approvals trickled in, until in June 2004 the twenty-second approval was received. The last study follow-up visit was conducted in November of 2004.

2.2 Organization of Part I

Chapter 2 Introduction

This chapter puts the SARS outcomes study into the context of the rapidity with which the outbreak evolved and describes the structure of this part of the thesis. The description of chapters 3-6 are in the form of the abstract that appeared with the published article.

Chapter 3 Background (SARS outcomes study)

Severe Acute Respiratory Syndrome (SARS) became a global epidemic in 2003. Comprehensive information on one-year outcomes and health care utilization is lacking. Research conducted during the SARS outbreak may help inform research planning for future public health emergencies. The objective of this study was to evaluate the one-year outcomes in survivors of SARS and their family caregivers.

Chapter 4 Methods (SARS outcomes study)

The study was prospective and observational. We evaluated 117 SARS survivors from Toronto, Ontario. Patients were interviewed and underwent physical examination, pulmonary function testing, chest radiography, a six-minute-walk test, quality-of-life
measures, and self-report of health care utilization. At one year, informal caregivers were identified for a survey on caregiver burden.

**Chapter 5 Results (SARS outcomes study)**

The enrolled survivors of SARS were young (median age, 42 years), and most were women (67%) and health care workers (65%). At one year after hospital discharge, pulmonary function measures were in the normal range, but 18% of patients had a significant reduction in distance walked in 6 minutes. The Medical Outcomes Study 36-Item Short Form Health Survey (SF-36®) domains were 0.3 to 1.0 SD below normal at one year. Of the patients, 17% had not returned to work by one year. Fifty-one patients required 668 visits to psychiatry or psychology practitioners. During the SARS epidemic, informal caregivers reported a decline of 1.6 SD below normal on the mental component score of the SF-36®.

**Chapter 6 Conclusion (SARS outcomes study)**

Most SARS survivors had good physical recovery from their illness, but some patients and their caregivers reported a significant reduction in mental health one year later. Strategies to ameliorate the psychological burden of an epidemic on the patient and family caregiver should be considered as part of future pandemic planning.

**Chapter 7 Importance of the SARS outcomes study & transition to part II**

This short chapter restates the importance of the SARS outcome study in the relation to the rest of the thesis and provides a transition to Part II of the thesis.
CHAPTER 3: SARS OUTCOMES STUDY: BACKGROUND

3.1 Introduction

Severe acute respiratory syndrome (SARS) became a global epidemic in 2003. Most cases were in Asia, and the largest concentration of North American cases occurred in Toronto, Ontario. Research efforts during and after the epidemic focused on the epidemiologic features of the illness, the detailed characterization of the pathogen, the clinical course, and the short-term outcomes of the acute disease. The longer-term physical and psychological consequences of SARS were not reported until recently. Several investigations of these longer-term outcomes (6 months) have focused on pulmonary function, distance walked in 6 minutes, and health-related quality of life (QOL). To date, in patients with SARS, there is little information on the pattern of return to work, exercise tolerance, or health care utilization after the SARS episode. Also, there have been no reports to our knowledge on the impact of this acute illness on the family caregiver. The goals of this study were to conduct a comprehensive and family-centered evaluation of the 1-year outcomes in survivors of SARS and their family caregivers.

3.1.1 Setting

The hospitals providing acute care to patients with SARS are located in the greater Toronto area, Ontario. This is an urban area of approximately 5.3 million people encompassing a geographic area of 7000km², the largest urban area in Canada, and the fifth largest in North America. The follow-up clinic was located at a quaternary care hospital in downtown Toronto.
CHAPTER 4: SARS OUTCOMES STUDY: METHODS

4.1 Methods

4.11 Study Design

Patients with SARS were referred to the longitudinal study by their acute care physicians. Discharge from hospital occurred between March 26, 2003, and August 22, 2003. Patient contact information was forwarded to the research site by the treating physician or hospital after their research ethics board had approved the protocol. Referred patients were eligible to participate if they were at least 16 years of age, had suspect or probable SARS according to Health Canada definitions, and lived in Ontario. Patients were excluded if they had negative convalescent serologic findings for the SARS coronavirus (n=17) or if they did not speak English (n=5). The research ethics boards at 20 participating institutions approved the protocol. All patients gave written informed consent.

4.12 Baseline Hospital Information

Baseline demographic data (described by Muller et al. 34) included clinical and treatment variables, length of hospital stay, and need for intensive care. Patients were also asked about their job status (health care worker or not), education, and history of lung disease.

4.13 Follow-up Protocol

We evaluated patients 3, 6, and 12 months after hospital discharge. At each visit, SARS survivors were interviewed and underwent physical examination, a standardized
Figure 4.1 Enrollment of Patients with Severe Acute Respiratory Syndrome (SARS) and Follow-up for Twelve Months after Discharge from Hospital

- 387 SARS patients in Toronto
  - 329 adults survived
  - 46 died
  - 12 children
  - 22 convalescent serology negative for SARS coronavirus (17 seen in clinic)

- 307 eligible
  - 198 physician referrals to our clinic
    - 84 enrolled at 3-month visit
      - 2 withdrawn
    - 107 enrolled by 6-month visit (100 seen)
      - 8 more withdrew
    - 117 enrolled by 12-month visit (107 seen)
      - 17 patients seen once
      - 26 patients seen twice
      - 74 patients seen 3 times
    - 58 refused consent
    - 22 new ones
    - 15 unable to contact
    - 3 out of province
    - 5 did not speak English

6-minute walk test[^35], pulmonary function testing, chest radiography, and convalescent SARS coronavirus serologic testing. They were systematically asked if they were experiencing cough, shortness of breath, alopecia, difficulty sleeping, myalgia, malaise, and fatigue. Two QOL instruments were administered. Participants were asked at each visit about health care
utilization. At 1 year after discharge, survivors were offered a stage-1 cardiopulmonary exercise test. They were also asked if they had a close family member or friend who assisted with their care in the early recovery period once their isolation was lifted. Informal caregivers were given questionnaires (Table 4.1) about how caring for a patient with SARS affected their lives.

### 4.14 Quality of Life (QOL) Measures

#### Table 4.1 Caregiver Questionnaire Characteristics

<table>
<thead>
<tr>
<th>Instrument</th>
<th>Scoring</th>
<th>SARS Caregiver Scores</th>
<th>Comparison Scores</th>
</tr>
</thead>
<tbody>
<tr>
<td>SF-36® 36</td>
<td>↑ score = better health-related quality of life (mean=50; SD=10)</td>
<td>PCS*=52</td>
<td>US 37 &quot;healthy&quot; PCS*=55</td>
</tr>
<tr>
<td></td>
<td></td>
<td>MCS† =34</td>
<td>US 37 Angina patients PCS*=36</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>US 37 &quot;healthy&quot; MCS†=53</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>US 37 Clinically depressed</td>
</tr>
<tr>
<td>Caregiver Assistance Scale (CAS) 38</td>
<td>↑ score = more assistance performed (range=0-102)</td>
<td>29</td>
<td>Caregivers for patients with Stroke 39 =47</td>
</tr>
<tr>
<td>Caregiver Impact Scale (CIS) 38</td>
<td>↑ score = more lifestyle interference (range=0-84)</td>
<td>22</td>
<td>Caregivers for patients with Stroke 39 =29</td>
</tr>
<tr>
<td>Personal Gain Scale 40 (PGS)</td>
<td>↑score = inner growth, gains in self-confidence and/or greater appreciation for one's own abilities (range= 4-16)</td>
<td>12</td>
<td>Caregiver for patients with ARDS 41 =12</td>
</tr>
<tr>
<td>Pearlin and Schooler 40, 7-item scale</td>
<td>↑ Mastry score = more individual sense of control over one’s own life (range, 7-28)</td>
<td>18</td>
<td>Caregivers for patients with stroke 39 = 19</td>
</tr>
<tr>
<td>Social support survey 42</td>
<td>↑ Score = more social supports (range 0-100)</td>
<td>67</td>
<td>Caregiver for patients with ARDS 41 =73</td>
</tr>
</tbody>
</table>

*PCS = Physical Component Summary Score  
†MCS = Mental Component Summary Score
The Medical Outcomes Study 36-Item Short Form Health Survey (SF-36®) is a widely used and extensively validated generic QOL measure that consists of 8 multiple-item domains. \(^{43}\) Scores are normalized to a mean ± SD of 50 ± 10, and 2 summary scores are calculated. \(^{36}\)

The St George’s Respiratory Questionnaire\(^{44}\) is a pulmonary disease-specific QOL measure that captures symptoms, activity, and impacts scores as subscales. Scores range from 0 to 100, with higher numbers indicating poorer QOL. A difference of 4 points is clinically significant. The questionnaire has been validated in many lung disorders. \(^{45-47}\)

4.15 Health Care Utilization

At each appointment, patients were asked about visits to their general practitioner or specialists, tests performed, and hospitalizations. Referrals initiated by our team were included in the health care utilization numbers.

4.16 Caregiver Questionnaires

An introductory letter, consent form, and questionnaires were sent to caregivers identified by the SARS survivors at 1 year after hospital discharge. The amount of care provided was assessed by the 17-item Caregiver Assistance Scale. \(^{38}\) The 14-question Caregiving Impact Scale measures the current level of lifestyle interference associated with providing care. \(^{38}\) Personal gain (4 items) is a positive outcome of providing care and represents caregivers’ inner growth, including gains in self confidence or obtaining greater appreciation for their abilities. \(^{40}\) Mastery, an individual’s sense of control over her or his life, was assessed by the 7-item measure from Pearlin and Schooler. \(^{48}\) The amount of social
support was evaluated using the Social Support Survey, which contains 19 questions.\textsuperscript{42} A higher score indicates a higher level of the parameter measured.

4.2 Statistical Analysis

The primary outcome measure of the study was the 6-minute walk distance at 3, 6, and 12 months. Sample size and power calculations were not feasible owing to the lack of published data on long-term outcomes and survival for this new illness. We summarized continuous variables as medians and interquartile ranges and compared them between groups using the Wilcoxon rank sum test. Categorical variables were summarized using proportions and 95\% confidence intervals and compared between groups using Pearson $\chi^2$ or Fisher exact test as appropriate. Multivariable regression analysis was not performed because of limited statistical power. The relationship between caregiver measures was analyzed using correlation coefficients.
CHAPTER 5: SARS OUTCOMES STUDY: RESULTS

5.1 Characteristics of the Patients

A total of 198 adults who were seropositive for the SARS coronavirus (at least 28 days after symptoms began) were referred to our clinic, and 117 patients were enrolled (Figure 4.1). It is not known why all eligible patients were not referred to us. Of those enrolled, 84 patients (72%) were seen at 3 months, 100 patients (88%) were evaluated at 6 months, and 107 patients (91%) were followed up to 1 year after hospital discharge. The atypical trend of increasing numbers was due to the unusual nature of an outbreak in which all patients fall ill in a very short time. Patient contact information became available to us about 3 to 8 months after acute illness. Median follow-up time for the 3-, 6-, and 12-month visits was 3.5, 7.1, and 12.5 months, respectively. No patient died during the year of follow-up. Home assessments were conducted for 2 patients at 6 months and for 8 patients at 1 year. More patients in the study cohort were health care workers and had received systemic corticosteroids and fewer had at least 1 preexisting medical condition, but they were otherwise similar to the 307 adult survivors of SARS in Toronto (Table 5.1). The median age of our cohort was 42 years, 67% of the subjects were female, and 65% were health care workers. The cohort was highly educated. Two of the enrollees were not admitted to the hospital. The median length of hospital stay was 14 days. Of the patients, 16% required admission to the intensive care unit (ICU) for a median of 10 days, 9% of whom required mechanical ventilation. Of the 117 patients, 62% received systemic corticosteroids, 60% received ribavirin, 9% received interferon, and 11% of patients did not receive treatment with any of these agents.
Table 5.1 Characteristics of Patients with Severe Acute Respiratory Syndrome (SARS) at Discharge from Hospital – Comparison of Enrolled Patients and Non-Enrolled Patients

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Enrolled Patients (n=117)</th>
<th>Non-enrolled Patients (n=187*)</th>
<th>p value†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age – years</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>42</td>
<td>44</td>
<td>0.13</td>
</tr>
<tr>
<td>Interquartile range</td>
<td>33-51</td>
<td>34-57</td>
<td></td>
</tr>
<tr>
<td>Female sex – no. (%)</td>
<td>78 (67%)</td>
<td>120 (64%)</td>
<td>0.66</td>
</tr>
<tr>
<td>Healthcare worker – no. (%)</td>
<td>76 (65%)</td>
<td>58 (31%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Education</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>University degree or more</td>
<td>90 (78%) ‡</td>
<td>N/A §</td>
<td>- -</td>
</tr>
<tr>
<td>Less than university degree</td>
<td>26 (22%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>At least one pre-existing medical condition</td>
<td></td>
<td>11 (9%)</td>
<td>34 (18%) ¶</td>
</tr>
<tr>
<td>History of previous lung disease</td>
<td>20 (17%) ‡</td>
<td>N/A §</td>
<td>- -</td>
</tr>
<tr>
<td>Ever smoked – no. (%)</td>
<td>20 (17%) ‡</td>
<td>N/A §</td>
<td>- -</td>
</tr>
<tr>
<td>Hospital length of stay – days</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>14</td>
<td>11</td>
<td>0.08</td>
</tr>
<tr>
<td>Interquartile range</td>
<td>8-19</td>
<td>8-17</td>
<td></td>
</tr>
<tr>
<td>Need for ICU stay- no. (%)</td>
<td>19 (16%)</td>
<td>29 (16%)</td>
<td>0.87</td>
</tr>
<tr>
<td>Median length of stay - days</td>
<td>10</td>
<td>14</td>
<td>0.97</td>
</tr>
<tr>
<td>Interquartile range</td>
<td>7-19</td>
<td>4-26</td>
<td></td>
</tr>
<tr>
<td>Need for mechanical ventilation - no. (%)</td>
<td>10 (9%)</td>
<td>17 (9%)</td>
<td>0.87</td>
</tr>
<tr>
<td>Medication administered</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systemic corticosteroids</td>
<td>72 (62%)</td>
<td>84 (45%)</td>
<td>0.05</td>
</tr>
<tr>
<td>Ribavirin</td>
<td>70 (60%)</td>
<td>102 (55%)</td>
<td>0.37</td>
</tr>
<tr>
<td>Interferon</td>
<td>11 (9%)</td>
<td>9 (4%)</td>
<td>0.12</td>
</tr>
<tr>
<td>None of the above</td>
<td>13 (11%)</td>
<td>40 (21%)</td>
<td>0.36</td>
</tr>
<tr>
<td>Weight loss</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median percent of body weight lost</td>
<td>9% **</td>
<td>N/A §</td>
<td>- -</td>
</tr>
<tr>
<td>Interquartile range</td>
<td>5%-11%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alopecia – no. (%)</td>
<td>78 (67%) ††</td>
<td>N/A §</td>
<td>- -</td>
</tr>
</tbody>
</table>

* Charts for 3 patients could not be retrieved
† Continuous variables are compared using Wilcoxon scores (Mann-Whitney U test) and categorical variables using Mantel-Haenszel Chi-Square
‡ Unknown in 1 patient
§ N/A=not available
¶ Includes diabetes mellitus, chronic renal failure, hepatitis B, chronic obstructive pulmonary disease, coronary artery disease, congestive heart failure, active cancer, connective tissue disease, HIV/AIDS, or transplantation
¶¶ Unknown in 2 patients
** Unknown in 3 patients
†† Unknown in 5 patients
5.2 Global Assessment

Patients self-reported a median loss of 9% of their body weight during acute care hospitalization. Of the patients, 67% reported alopecia; it resolved in most patients by 6 months and was not significantly associated with ribavirin administration in this limited sample ($\chi^2=0.59; p=.44$). Chest radiographs were normal or had returned to pre-SARS baseline in all patients by one year, with the exception of one long-stay ICU survivor whose radiographs continued to show small lung volumes, fibrosis, and ground glass opacities beyond 1 year. Abnormalities on respiratory examination including wheezes, crackles, and tachypnea were found in 14%, 4%, and 2%, respectively, at the 3 visits. Fatigue (64%, 54%, and 60%) and difficulty sleeping (47%, 50%, and 44%) were commonly reported at the 3-, 6-, and 12-month time points, respectively. Patients also frequently mentioned shortness of breath (44%, 49%, and 45%) at the 3-, 6-, and 12-month follow-up visits, respectively. Only 12%, 18%, and 13% of patients stated that they were asymptomatic at the 3-, 6-, and 12-month visit. All SARS survivors who were mechanically ventilated reported muscle wasting and weakness at the time of hospital discharge. Three patients had new reactive airways disease. Two patients had entrapment neuropathies, 2 patients had hoarseness after prolonged intubation, and 1 patient had heterotopic ossification and discomfort at old chest tube sites.

5.3 Six-minute Walk Distance and Pulmonary Function

At 3 months, SARS survivors had a normal median 6-minute walk distance (81% of that predicted for an age and sex-matched control population). A reduced walking distance was present in 31% of patients at 3 months and in 18% at 1 year (Table 5.2). There was no
relationship between 6-minute walk distance and exposure to steroids, burden of comorbid illness, preexisting pulmonary dysfunction, or degree of weight loss. For most patients, spirometry, lung volume measures, and diffusion capacity were within normal limits at 3 months and remained normal for the duration of follow-up (Table 5.2). Patients admitted to the ICU had evidence of restrictive disease at 3 and 6 months after hospital discharge but had normal pulmonary function by one year. One long-stay ICU patient had moderate restrictive lung disease that persisted beyond the one-year follow-up.

5.4 Patient Quality of Life (QOL)

All SF-36 domains were significantly reduced at 3 months with the exception of bodily pain. Role physical, social function, and role emotional domains were improved at one year after hospital discharge but did not normalize. General health, vitality, and social functioning domains remained 1.0, 0.8, and 0.8 SDs below the normal range at one year after hospital discharge, respectively (Figure 5.1).

The St George’s Respiratory Questionnaire total and domain scores indicated decreased QOL at 3 months that persisted at 1 year, despite some improvement from 3 to 6 months (Table 5.2).
Table 5.2. Ability to Exercise, Pulmonary Function, Return to Work and Quality of Life as Reported on the St. George’s Respiratory Questionnaire in Patients with Severe Acute Respiratory Syndrome (SARS) during the 12 months following Discharge from Hospital

<table>
<thead>
<tr>
<th></th>
<th>3 Months (n=84)</th>
<th>6 Months (n=100)</th>
<th>12 months (n=107)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Distance walked in 6 minutes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median – metres</td>
<td>483</td>
<td>487</td>
<td>488</td>
</tr>
<tr>
<td>Interquartile range – metres</td>
<td>(396-552)</td>
<td>(447-553)</td>
<td>(448-555)</td>
</tr>
<tr>
<td>Percentage of predicted value *</td>
<td>81%</td>
<td>81%</td>
<td>83%</td>
</tr>
<tr>
<td>Pulmonary Function Testing</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Forced vital capacity (% of predicted)</td>
<td>98 (89-113)</td>
<td>103 (91-115)</td>
<td>103 (92-115)</td>
</tr>
<tr>
<td>Forced expiratory volume in one second (% of predicted)</td>
<td>107 (94-120)</td>
<td>110 (100-122)</td>
<td>109 (96-122)</td>
</tr>
<tr>
<td>Total lung capacity (% of predicted)</td>
<td>98 (88-111)</td>
<td>101 (93-112)</td>
<td>102 (92-112)</td>
</tr>
<tr>
<td>Residual volume (% of predicted) **</td>
<td>101 (75-112)</td>
<td>98 (82-115)</td>
<td>96 (83-113)</td>
</tr>
<tr>
<td>Carbon monoxide diffusion capacity (% of predicted) ** ††</td>
<td>87 (77-93)</td>
<td>86 (80-93)</td>
<td>85 (81-93)</td>
</tr>
<tr>
<td>Maximum inspiratory pressure (% of predicted) **</td>
<td>68 (49-89)</td>
<td>74 (59-105)</td>
<td>78 (65-110)</td>
</tr>
<tr>
<td>Maximum expiratory pressure (% of predicted) **</td>
<td>48 (40-61)</td>
<td>54 (43-67)</td>
<td>56 (45-73)</td>
</tr>
<tr>
<td>Return to work</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Full-time work – no. (%)</td>
<td>25 (30%)</td>
<td>53 (53%)</td>
<td>71 (66%)</td>
</tr>
<tr>
<td>Pre-SARS level of work – no. (%)</td>
<td>35 (42%)</td>
<td>63 (63%)</td>
<td>79 (74%)</td>
</tr>
<tr>
<td>Not returned to work – no. (%)</td>
<td>41 (49%)</td>
<td>17 (17%)</td>
<td>18 (17%)</td>
</tr>
<tr>
<td>St. George’s Respiratory Questionnaire ‡‡</td>
<td>n=75</td>
<td>n=83</td>
<td>n=89</td>
</tr>
<tr>
<td>Total score (normal=6)</td>
<td>24 (8-36)</td>
<td>17 (6-34)</td>
<td>18 (5-34)</td>
</tr>
<tr>
<td>Symptoms score (normal=12 §§)</td>
<td>20 (8-35)</td>
<td>15 (4-36)</td>
<td>18 (5-40)</td>
</tr>
<tr>
<td>Activity score (normal=9 §§)</td>
<td>36 (12-60)</td>
<td>31 (6-60)</td>
<td>29 (3-54)</td>
</tr>
<tr>
<td>Impact score (normal=2 §§)</td>
<td>14 (2-29)</td>
<td>9 (2-25)</td>
<td>10 (2-25)</td>
</tr>
</tbody>
</table>

* normal values were calculated in an age-sex-matched population according to the method of Enright and Sherrill.
† 9 patients missed this test
‡ 6 patients missed this test
§1 patients failed to present to the lab
¶ 1 patient failed to present to the lab, 1 felt ill and refused, 1 becomes ill with testing, so refused
¶¶ 1 patient failed to present to the lab, 1 unable, 1 refused, 1 becomes ill with testing, so refused.
** These variables could not be assessed during home visits.
†† Carbon monoxide diffusion capacity was not corrected for haemoglobin.
‡‡ Lower scores indicate a better quality of life; some patients did not return the questionnaire.
§§ Normal values as per Jones PW et. al.
Figure 5.1  Mean Health-Related Quality of Life (QOL) Scores among Patients with Severe Acute Respiratory Syndrome (SARS) in the 12 months following Hospital Discharge (A) and their Caregivers just after Quarantine (B)

PCS=physical component summary score; MCS=mental component summary score
5.5 Return to Work

Many patients initially returned to work part-time, gradually increasing their workload over 1 to 2 months. Only 23 patients returned to work full-time with no need for a modified schedule. Those who required a modified workload took a median of 94 days to return to any work. At 1 year, 17% of patients had not returned to work, and a further 9% had not returned to their pre-SARS level of work (Table 5.2).

5.6 Health Care Utilization

Health care utilization of SARS survivors during the first year after hospital discharge was substantial (Table 5.3). Psychiatric evaluation accounted for the greatest number of visits. Of the patients, 74% saw their primary care physician a median of 5 times. Infectious disease specialists assessed 72% of patients, mostly in the first 3 months after discharge. Four patients were readmitted to acute care hospitalization within days of discharge, and two patients were admitted months later for non-SARS related issues. Three patients needed inpatient rehabilitation, and 4 had surgery over the course of the follow-up year.

5.7 Caregiver Survey

Seventy-two patients identified informal caregivers; two did not have adequate proficiency in English to complete the surveys. Forty-six surveys were returned for a participation rate of 66% (46/70). The caregivers were highly educated. The caregiver was usually the patient’s spouse (72%), and was most often female (57%) (Table 5.4). Significantly fewer patients had returned to work in the responder group (p=.009); this is
likely because people who recovered quickly and went back to work early had fewer needs, and so either these patients did not identify a caregiver or caregivers believed that they had not provided any care giving (Table 5.4). The summary score of the physical components of the SF-36 for caregivers was normal compared with an age- and sex-matched Canadian population. However, the mental component score was significantly below normal and was significantly correlated with the degree of lifestyle interference and loss of control reported by the caregiver (Pearson r=−0.6; P < .001 for both). The greatest decrements in caregiver SF-36 scores were in the mental health and social functioning domains (Figure 5.1). Caregivers reported a score of 29 of a possible 102 on the Caregiver Assistance Scale and 22 of 84 on the Caregiving Impact Scale. They reported a high level of personal gain (12/16) and a mid-range sense of control (18/28) over their own lives once quarantine and isolation were lifted. Social support was rated at 67 of a possible 100. Table 4.1 summarizes these results and presents scores obtained from caregiver studies with patients experiencing other illnesses for comparison.
### Table 5.3. Health Care Utilization in Patient with Severe Acute Respiratory Syndrome (SARS) in the Year Following Discharge from Acute Hospital

<table>
<thead>
<tr>
<th>Medical Consultations:</th>
<th>Total Utilization</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total number of visits</td>
<td>Number of patients</td>
</tr>
<tr>
<td>Psychiatric</td>
<td>668</td>
<td>51</td>
</tr>
<tr>
<td>Psychiatrist</td>
<td>173</td>
<td>24</td>
</tr>
<tr>
<td>Support group</td>
<td>255</td>
<td>23</td>
</tr>
<tr>
<td>Psychologist</td>
<td>119</td>
<td>11</td>
</tr>
<tr>
<td>Social worker</td>
<td>60</td>
<td>10</td>
</tr>
<tr>
<td>Other*</td>
<td>61</td>
<td>10</td>
</tr>
<tr>
<td>Family practitioners</td>
<td>468</td>
<td>86</td>
</tr>
<tr>
<td>Infectious disease specialist †</td>
<td>196</td>
<td>84</td>
</tr>
<tr>
<td>Respirologist</td>
<td>25</td>
<td>11</td>
</tr>
<tr>
<td>Sleep studies</td>
<td>5</td>
<td>3</td>
</tr>
<tr>
<td>Physiatrist</td>
<td>16</td>
<td>9</td>
</tr>
<tr>
<td>Osteoporosis specialist</td>
<td>8</td>
<td>6</td>
</tr>
<tr>
<td>Neurologist</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Other medical specialists ‡</td>
<td>77</td>
<td>30</td>
</tr>
<tr>
<td>Rehabilitation services</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intense specialized program §</td>
<td>N/A</td>
<td>9</td>
</tr>
<tr>
<td>Hospital sponsored program ‖</td>
<td>229</td>
<td>20</td>
</tr>
<tr>
<td>Private</td>
<td>571</td>
<td>2</td>
</tr>
<tr>
<td>occupational/physiotherapy</td>
<td>12</td>
<td></td>
</tr>
<tr>
<td>Home rehab service</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diagnostic tests ¶</td>
<td>502</td>
<td>90</td>
</tr>
<tr>
<td>Homecare</td>
<td>91</td>
<td>5</td>
</tr>
<tr>
<td>Acute care admissions ††</td>
<td>6</td>
<td>5</td>
</tr>
<tr>
<td>Emergency room</td>
<td>5</td>
<td>4</td>
</tr>
<tr>
<td>Surgeries **</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>Rehabilitation centre admissions ‡‡</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Other miscellaneous services §§</td>
<td>12</td>
<td>6</td>
</tr>
</tbody>
</table>

### Medical Consultations Initiated by Our Clinic Personnel

<table>
<thead>
<tr>
<th></th>
<th>Number of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Psychiatric</td>
<td>17</td>
</tr>
<tr>
<td>Respiratory/sleep assessment</td>
<td>2</td>
</tr>
<tr>
<td>Physiatry</td>
<td>5</td>
</tr>
<tr>
<td>Osteoporosis Assessment</td>
<td>6</td>
</tr>
<tr>
<td>Neurology/neuro-cognitive testing</td>
<td>3</td>
</tr>
<tr>
<td>Referrals to other medical specialties ‖‖</td>
<td>11</td>
</tr>
<tr>
<td>Referrals to other professionals/services ¶¶</td>
<td>11</td>
</tr>
</tbody>
</table>
* includes employee assistance program, occupational health counselor, relaxation therapy
† most often within the first month after discharge
‡ gastroenterology, internal medicine, asthma clinic, cardiology, dermatology, endocrinology, obstetrics/gynecology, kinesiology, oncology, ophthalmology, orthopaedics, plastic surgery, nephrology, rheumatology, general surgery, urology, vascular surgery
§program initiated by the workers compensation board consisting of assessment by a physiatrist, physiotherapist, occupational therapist, and a psychiatrist. Treatment was 3-4 full days/week by whichever specialists were deemed required and for as many weeks as needed.
‖ program initiated by one hospital that had many health care workers affected, group met once a week for many months
¶ most frequently used are chest x-rays and blood tests
** 1 hip fracture repair, 1 hip replacement for avascular necrosis and 1 cataract removal and 1 repair of an old shoulder injury
†† 4 of these were within 10 days of initial discharge
‡‡ 2 were directly from the SARS acute hospitalization; 1 was after hip fracture repair in a post-transplant patient
§§ includes immunizations, massage therapy, speech therapy, dietician, O₂ tank, arthroplasty knee, and nurse practitioner
‖‖ otolaryngology, general surgery, cardiology, nephrology, orthopaedics, rheumatology, thoracic surgery, thrombosis clinic
¶¶ diagnostic testing, pharmacy, wig specialist, speech pathology
Table 5.4. Characteristics of Caregivers of Patients with Severe Acute Respiratory Syndrome (SARS) and Comparison of Patient Demographics of Enrolled Caregivers versus Total Cohort

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>n=46</th>
<th>Median (Interquartile range)</th>
<th>Caregiver Sample (n=46)</th>
<th>Not in Caregiver sample * (n=26)</th>
<th>no caregiver identified (n=28)</th>
<th>p-value †</th>
</tr>
</thead>
<tbody>
<tr>
<td>Caregiver sex – female – no. (%)</td>
<td>26 (57%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Caregiver age – years</td>
<td>50 (37-58)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Relationship to patient – no. (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Spouse (58% of these were male)</td>
<td>33 (72%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sister</td>
<td>5 (11%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mother</td>
<td>5 (11%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>3 (6%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Caregiver also had SARS – no. (%)</td>
<td>5 (11%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Caregiver SF-36® summary scores</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Physical component</td>
<td>52±11</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mental component</td>
<td>34±16</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patient age at hospital discharge – years</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>45</td>
<td></td>
<td>39</td>
<td>41</td>
<td></td>
<td>0.44</td>
</tr>
<tr>
<td>Interquartile range</td>
<td>37-53</td>
<td></td>
<td>31-49</td>
<td>33-52</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patient sex – female – no. (%)</td>
<td>32 (70%)</td>
<td></td>
<td>18 (69%)</td>
<td>17 (61%)</td>
<td></td>
<td>0.88</td>
</tr>
<tr>
<td>Patient is health care worker – no. (%)</td>
<td>31 (67%)</td>
<td></td>
<td>13 (50%)</td>
<td>21 (75%)</td>
<td></td>
<td>0.21</td>
</tr>
<tr>
<td>Hospital length of stay – days</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>14</td>
<td></td>
<td>15</td>
<td>12</td>
<td></td>
<td>0.56</td>
</tr>
<tr>
<td>Interquartile range</td>
<td>8-19</td>
<td></td>
<td>10-18</td>
<td>7-21</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Need for ICU stay – no. (%)</td>
<td>7 (15%)</td>
<td></td>
<td>5 (19%)</td>
<td>4 (14%)</td>
<td></td>
<td>0.69</td>
</tr>
<tr>
<td>Median length of stay - days</td>
<td>19</td>
<td></td>
<td>8</td>
<td>8</td>
<td></td>
<td>0.05</td>
</tr>
<tr>
<td>Intersquartile range</td>
<td>10-56</td>
<td></td>
<td>7-17</td>
<td>5-9</td>
<td></td>
<td></td>
</tr>
<tr>
<td>At least one pre-existing medical condition</td>
<td>6 (13%)</td>
<td></td>
<td>2 (8%)</td>
<td>1 (7%)</td>
<td></td>
<td>0.42</td>
</tr>
<tr>
<td>Medication administered – no. (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systemic corticosteroids</td>
<td>25 (54%)</td>
<td></td>
<td>18 (69%)</td>
<td>20 (71%)</td>
<td></td>
<td>0.16</td>
</tr>
<tr>
<td>Ribavirin</td>
<td>26 (57%)</td>
<td></td>
<td>13 (50%)</td>
<td>17 (61%)</td>
<td></td>
<td>0.66</td>
</tr>
<tr>
<td>Interferon</td>
<td>7 (15%)</td>
<td></td>
<td>2 (8%)</td>
<td>1 (4%)</td>
<td></td>
<td>0.23</td>
</tr>
<tr>
<td>None of the above</td>
<td>5 (11%)</td>
<td></td>
<td>3 (12%)</td>
<td>5 (18%)</td>
<td></td>
<td>0.98</td>
</tr>
<tr>
<td>Patient returned to full-time work by one year – no. (%)</td>
<td>25 (54%)</td>
<td></td>
<td>21 (81%)</td>
<td>21 (75%)</td>
<td></td>
<td>0.009</td>
</tr>
<tr>
<td>Patient SF-36® Score at 3 months – Mean ± s.d.</td>
<td>(n=35)</td>
<td>(n=16)</td>
<td>(n=14)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Physical Component</td>
<td>40 ± 11</td>
<td></td>
<td>39 ± 12</td>
<td>48±12</td>
<td></td>
<td>0.02</td>
</tr>
<tr>
<td>Mental Component</td>
<td>41 ± 14</td>
<td></td>
<td>37 ± 14</td>
<td>45±13</td>
<td></td>
<td>0.33</td>
</tr>
</tbody>
</table>
* A total of 100 patients were approached to identify a caregiver
† Continuous variables are compared using Wilcoxon scores (Mann-Whitney U test) and categorical variables using Mantel-Haenszel Chi-Square
‡ Includes diabetes mellitus, chronic renal failure, hepatitis B, chronic obstructive pulmonary disease, coronary artery disease, congestive heart failure, active cancer, connective tissue disease, HIV/AIDS, or transplantation
6.1 Discussion

To our knowledge, this is the largest prospective follow-up study of SARS survivors to one year. As with other SARS follow-up studies \(^{28,30,52}\), most patients had lung function that was within normal limits by three months after hospital discharge, and these normal results persisted to one year. The SARS ICU survivors had similar physical impairments to those described previously for acute respiratory distress syndrome (ARDS) survivors. \(^{53}\) All ICU survivors had restrictive disease at three months, consistent with the findings of the Singapore \(^{54}\) and Taiwanese \(^{55}\) groups, and pulmonary function rose into the normal range by one year after hospitalization. Despite normal pulmonary function testing, normal exercise capacity, and a minority of patients (18%) with a clinically important reduction in distance walked in six minutes, many patients continued to report shortness of breath and fatigue as notable contributors to exercise limitation at one year.

The persistence of symptoms and perception of physical limitations were reflected in the QOL measures at one year. Of the survivors, 37% were still reporting an important reduction in their physical health (at least 1 SD below normal on the physical component summary score of the SF-36®) at one year after acute care hospitalization. As reported by Ong et al. \(^{29}\) and our study, scores on the St George’s Respiratory Questionnaire also confirmed a decreased QOL related to pulmonary symptoms. It is possible that the persistent symptoms of shortness of breath and fatigue may reflect a subtle degree of respiratory muscle weakness and a perceived increase
in the work of breathing, but the exact pathophysiologic mechanism of these complaints remains unclear. Of the patients with SARS, 33% reported a significant decrement in mental health at one year (at least 1 SD below normal on the mental component summary score) and the health care utilization data suggest an important need for psychological counseling and support after hospitalization.

During the clinic visits, we had an opportunity to talk with patients and to understand the stressors that they experienced during this illness. Many patients experienced social stigmatization and loss of anonymity through the media, death of close family members and coworkers, and the inability to be present at the time of death or attend funeral services because of quarantine, isolation, or hospitalization. Several described the emotional strain of quarantine and isolation. Others described overwhelming fear for their physical health and a deep concern about the possibility of transmission to family or loved ones. Patients with SARS were subjected to extraordinary stressors during and after the outbreak and experienced significant emotional consequences as a result. Psychological trauma to patients and caregivers may have been reduced had their mutual support system remained intact through the outbreak, and this may have been achieved through video conferencing technology via the Internet. Telephone contact may also have helped but was not available in all circumstances because of the constraints of isolation rooms. Access to television and newspapers may also have helped those in hospital retain a sense of connectedness to the outside world. Early on in the SARS outbreak, the mode of transmission of the disease was unknown, and all person-to-person contact was minimized. However, some patients reported that health care workers insisted on spending time with and giving emotional support to them, and this helped to ameliorate their feelings of fear, anxiety, and isolation.
Acute illness affects the family as well as the patient. Caregivers told us that while their physical health remained at the level of the population average, the emotional impact of having a family member with an unknown illness was significant. Caregivers scored 1.6 SDs below the normal value expected for their age and sex on the mental component summary score of the SF-36® when asked to recall their feelings from the post-isolation period. The caregivers of SARS survivors provided assistance after the isolation period to an extent similar to the caregivers of patients with ARDS at two years after ICU discharge. Personal gain and perceived mastery of their situations were comparable in the SARS and ARDS cohorts, whereas ARDS caregivers believed that they had slightly more social support than did individuals caring for patients with SARS (Table 4.1).

Our study had several limitations. First, we enrolled only 38% of the entire Toronto population of adult survivors and 59% of those who were referred to us. Recruitment was challenging because many SARS survivors did not wish to be seen or discuss their experiences, and the members of our team were unknown to these patients. Our study sample contained an excess of health care workers, more patients who had at least one preexisting medical condition, and more who were treated with systemic corticosteroids. These facts, along with the high education levels and the number of women in both the patient and caregiver groups, may limit generalizability. The number of health care workers in the sample may also skew the utilization of health care services used, since health care workers are very aware of their own health status and may use services more than other workers in the population.

Second, the premorbid health status of patients and their caregivers and the health care utilization of patients were not documented, and perhaps some of the functional limitation and decreased QOL that we observed was attributable to preexisting health conditions and not directly
related to SARS. However, given the young age of both caregivers and patients and the fact that most were working prior to SARS, the likelihood of premorbid illness being a major contributor to the observed results seems minimal.

Third, the retrospective nature of the caregiver survey makes the caregiver information subject to recall bias. Finally, we were not able to include a control group in this study because of the unknown nature and outcome of this new infectious disease.

We have shown that most SARS survivors have pulmonary and functional recovery from their acute illness. However, one year after discharge from hospital, health-related QOL remained lower than in the general population, and patients reported important decrements in mental health. These findings are reflected in the notable utilization of psychiatric and psychological services in the one-year follow-up period. We have also demonstrated that family caregivers experienced considerable emotional distress during the acute illness of their family member. These data may help to highlight the needs of patients and caregivers during and after an epidemic, the potential benefit of a family-centered approach to follow-up care, and the importance of exploring strategies to minimize the psychological burden of an epidemic illness as part of future pandemic planning initiatives.

6.2 Acknowledgments

We dedicate this work to the memory of all patients with SARS who died during this worldwide epidemic and also to those patients and family members who endured this illness. We would also like to acknowledge the extraordinary efforts of the patients with SARS and their caregivers who so generously donated their time to participate in this study to help educate us
about how SARS affected their lives. We also wish to acknowledge the expertise and thoughtful contributions of Jim Brunton, BSc, MDCM, Reena Lovinsky, MD, FRCPC, and Peter Webster, MD, FRCPC, toward the successful completion of this project, and we thank Allan Detsky, MD, PhD, for encouraging us to pursue this study. We acknowledge the contribution of the members the Canadian SARS Research Network.
CHAPTER 7: IMPORTANCE OF THE SARS OUTCOMES STUDY

The SARS outcomes study documents the sequelae of SARS survivors one-year after the acute illness given the best supportive care possible while acknowledging that there was a lack of knowledge to guide this care. While studies of this type were undertaken in several countries (Hong Kong, Singapore, Taiwan and China)\(^{28,29,55-58}\), the Toronto study was the largest of its kind and the only one to include informal family caregivers in its analysis. All of the studies used quantitative methods and found similar results. Importantly, the mental health residua (despite near complete physical recovery) found in all studies of having suffered a contagious and stigmatizing illness both in patients and their caregivers may be generalizable to other infectious diseases.

The Toronto SARS outcomes study stands as an important contribution to the literature on its own, but in the context of this thesis, it was also important as a starting point for my critical reflection of the ethical issues encountered in the conduct of research during a public emergency. This outcomes study was conducted partially under emergency circumstances and illustrates the challenges of performing research during a public emergency. After its completion, I felt that I had gained a unique perspective on research conducted during an emergency, and I wanted to apply this perspective to explore the underlying ethical issues and their consequences.

Part I of this thesis is written in the style of a medical journal, and does not acknowledge difficulties that were encountered in the collection of these data or of any ethical issues that we encountered during the study. We did not address issues such as the infection control measures
that were in place and the language used reflects an assumption that there is nothing abnormal or problematic about this type of study. The conventions of writing scientific journal articles were unsatisfying. It did not allow me the flexibility to explore and include some of the issues that I knew were important and salient, but that were not easily quantifiable. To address this concern, I sought to complement the objective positivist account with an analytical reflection of the ethical issues that were encountered in the conduct of the SARS outcomes study. I wanted to reveal the context of the outbreak and account for the changes that were necessitated by it and explore any ethical implications resulting from these changes. Further, I wanted to discover what was already written about the conduct of research during a public emergency and integrate this with my own observations, in order to discuss these concerns in an academically rigorous fashion. Part II of the thesis is this analytical reflection. It consists of a description of the ‘case’ that was the SARS outcomes study and those things that ‘didn’t feel quite right’ as the study progressed. Each of these challenges is then mapped on to one or more ethical considerations that are then discussed in detail, particularly as they are related to the public emergency. These ethical issues include: resource allocation, recruiting vulnerable populations to participate in research projects and the social obligation to participate in research in a public emergency situation.
Part II

ETHICAL ISSUES ENCOUNTERED IN THE SARS OUTCOMES STUDY: AN ANALYTIC REFLECTION
CHAPTER 8: INTRODUCTION TO PART II

The purpose of part II is to explore the ethical issues that emerged during the planning and implementation of the SARS outcomes study and to discuss them in the context of other public emergencies.

8.1 Background

During the conduct of the SARS outcome study, we encountered challenging and novel problems. The speed with which the early events occurred seemed to be particularly important and led me to think about how research is inevitably conducted very differently in the context of an outbreak. For example, our study protocol was written very quickly and only possible because it was based largely on another completed study and there was no time to pilot procedures for feasibility. Similarly, our method of obtaining patient contact information was not well defined at the outset of the study. Problems of trying to conduct research too quickly during an epidemic are not new – Barry comments on this in his description of research conducted during the 1918-19 influenza epidemic as researchers struggled with some of these same issues: (pg 277)

“The pressure pushed [the researcher] to abandon more than his ambitious plans. He had always been meticulous, had never compromised ... always moving forward carefully, basing his own experiments upon well-established premises and with as few assumptions as possible.....Now he had no leisure for justification. If he was to have any impact on the course of the epidemic he would have to guess – and guess right.”

During the SARS outbreak, many health care workers (HCW) themselves fell ill and became eligible to participate in research studies. I wondered what the impact of contracting the
illness was on these health care workers that were doubly vulnerable since they were sick, and contracted the illness at work. It is unusual to form a research cohort of illness survivors who were mostly (65%) HCW. I also wondered if the dual role of researcher/clinician was special in this context. The consent process must have been influenced by the infection control measures that were in place. For example, was the important face-to-face interaction between research participant and research staff decreased by isolation, quarantine and the protective gear that all hospital workers wore for their own protection? I knew that privacy and confidentiality were different in an outbreak, having seen patients’ names in the media, but did the strict confidentiality rules normally adhered to still apply when it came to research? I wondered if research participants felt that we were intruding when we called them to describe the study to them. It was enormously frustrating to reach all the SARS survivors and I wondered if they felt pressured to be part of the study. I did not know if there was a social obligation to participate in any research and in particular research during a public emergency.

In order to examine these issues, first I describe the conduct of the SARS outcomes study and the things that ‘didn’t feel quite right’. These included the manner and timing in which we received the contact information about potential participants in the study and the fact that patients were asked to participate in multiple studies, some of which I did not know anything about. I then explicate the ethical issues that may have arisen from these challenges because of the context of the outbreak. I also look to the literature to discover what has been written about the conduct of research during a public emergency and integrate this with my own observations.

8.2 Organization of Part II
Chapter 8  Introduction to Part II

This current chapter provides an introduction to part II of the thesis and an outline of its organization.

Chapter 9  The ‘Case’ of the SARS Outcomes Study: It Didn’t Feel quite Right

Here, I discuss the problems I observed as the SARS outcomes study moved from its inception to completion. I delve deeper into the process of conducting the research project and the numerous times when things ‘didn’t feel quite right’ because of circumstances that were different and related to the context of the outbreak.

Chapter 10  Methods of the Analytical Reflection

The purpose of this chapter is to describe the methods used in this analytic reflection on the ethical issue encountered as I participated in the conduct of the SARS outcomes study described in part I.

Chapter 11  Ethical Issues Encountered in the SARS Outcomes Study

This chapter discusses the ethical issues that were encountered in the SARS outcomes study. Each of the challenges that were identified in chapter 9 is mapped on to one or more ethical considerations. I explore what others have written about the challenges that are faced in the ethical conduct of research. In particular, I sought references to research carried out during an outbreak or public emergency.

Chapter 12 Summary and Link to Part III
A brief summary of the ethical issues encountered in the SARS outcomes study is provided. After this review, I still had many unanswered questions. I foreshadow here, the reasons for the studies that follow in part III that were designed to answer some of these questions.
CHAPTER 9: ETHICAL ISSUES ENCOUNTERED: BACKGROUND

9.0 The ‘Case’ of the SARS Outcomes Study: It Didn’t Feel Quite Right

This chapter discusses the problems I observed as the SARS outcomes study moved from its inception to completion. Hoffmaster notes that “the contexts in which the moral problems of medicine arise can be appreciated only by becoming immersed in clinical [or research] settings” This is exactly what I had done in the conduct of the SARS outcomes study. The introduction to the thesis provides the big picture – SARS globally and across the city of Toronto and part I is a medical analysis of the patients as they recovered over the one-year following their acute illness. In this chapter, I delve deeper into the process of conducting the research project and the numerous times when things ‘didn’t feel quite right’ because of circumstances that were different, which were related to the context of the outbreak. These include: 1) writing the protocol with speed and little knowledge of the pathogen and the sequelae of the illness, 2) writing the consent forms before details of the protocol were finalized, 3) quick local REB approval and protracted multi-site REB approvals, 4) funding, 5) identifying and contacting potential participants, 6) recruiting potential participants from other hospitals, 7) obtaining informed consent from SARS survivors, and 8) carrying out the study procedures.

9.1 Preparation of the SARS Outcomes Study

During the preparation stage of the SARS Outcomes Study, the study team wrote the research proposal and consent forms, submitted and obtained enough REB approvals to begin
recruiting at the first sites and discussed funding (and lack thereof). This portion of the study took two to three months.

9.11 Writing the Protocol

The first step in the conduct of the SARS outcomes study was to write a scientifically acceptable protocol. Notwithstanding the many unknown parameters, the study team felt that the potential knowledge that might be gained was great, despite some uncertainty about the appropriateness of the selected outcome measures. The SARS outcomes study was written quickly and some aspects of the protocol reflected the limited knowledge about how the SARS virus affected patients. Ordinarily, before a large study is carried out, a pilot study helps to illuminate the logistical hurdles involved in the conduct of a study (e.g. sample size and recruitment strategies) and to determine what the relevant data collection strategy and outcomes should be. With the results of a pilot study in hand, researchers are able to refine the study protocol (i.e., recruiting strategies and feasibility of study interventions) to make it run more smoothly and to accurately predict the sample size required to answer the question posed with statistically significant results. This was the first occurrence of the feeling that ‘things didn’t feel quite right’—the speed and lack of reflection time in the writing of the protocol, despite having the template from a previous study.

The planning stages of the study occurred during the outbreak, in April and May of 2003. At that time, we did not have a sense of the size of the affected population or the duration of the outbreak. Our goal was to recruit all eligible adult SARS survivors in the Greater Toronto area. As the study evolved, we learned that this was an unrealistic goal—only 38% of the Toronto population of adult survivors and 59% of those who were referred to us were enrolled. This low
accrual may have been a result of survivors’ reluctance to have anything to do with a hospital system that some of them felt had failed them, or that would bring back memories of the horrendous experience of having had SARS, and the quarantine and isolation that all survivors lived through. Alternately, our failure to enroll a greater proportion of patients may have been because the study team could not approach survivors when they were still in-patients, since the protocol was not written in time. Researchers were also not permitted to enter hospitals other than their home institution. Scientific and social value and validity can potentially be compromised when a protocol is not practical, feasible or not given enough thought about the relevance of the potential findings in the context of the current knowledge base. These issues are discussed in further detail in the next chapter. The magnitude of these challenges might have been reduced had we had more planning and thinking time as the protocol was written.

9.12 Writing the Consent Forms

The second thing that was more challenging than usual was the process of writing the consent forms when so little was known about the illness and its sequelae. Two sections of the consent form were difficult to write; the background section and section on risks and benefits. The background section was challenging because the information available was changing daily. The risks and benefits of the follow-up study were unknown as the disease course and treatments had not been characterized. For instance, while we postulated that the risk to participants in our observational follow-up study would not be greater than the risks of the individual tests required (which we thought were not onerous), we were not totally certain of this. The composition of the consent form was complicated further by the inclusion of the SARS outcome study in the Canadian SARS Research Network (CSRN) group.
The CSRN was formed to facilitate the study of multiple aspects of the laboratory findings and clinical features in SARS patients. Included in the themes of this group were: immunology/ genetics, immunopathogenesis of the disease, clinical consequences of SARS (the outcomes study), psychological consequences of SARS, organ involvement at autopsy, epidemiology, and diagnosis of the disease. Each thematic group prepared one or several protocols that it felt was relevant and feasible and sent it to the Network office. Each researcher also submitted information relevant to his/her protocol(s) to be included in the consent form. This information was amalgamated into a single consent form covering all of the protocols and was written by personnel in the CSRN’s office. Thus, the consent form described many protocols simultaneously and patients were given options with tick boxes to indicate in which study they wished to participate. The outcomes group of investigators joined the Network later than other groups. This meant that the comprehensive consent form was ready prior to the finalization of the outcomes portion and therefore the SARS outcomes study section was not well described. In order to get REB approval as early as possible, this early consent form was submitted to our REB despite the lack of detail about the outcomes portion of the study. Once details of the study were available, a separate consent form discussing only the long-term outcomes portion of the Network’s protocol was put together. Unfortunately, this meant that patients who wanted to be part of the outcomes study as well as other aspects of the Network’s work had to sign two consent forms. While we did not want to discourage people from taking part in the research with multiple long and complicated forms and perhaps compromising the validity of the projects, I felt that the extra burden of two forms was made up for by the critical information provided in the second form which was purposefully kept short and simple. Both consent forms are included in Appendix I.
9.13 Obtaining REB Approval

Once the protocol and consent forms were written, they were sent to the REB. At the University Health Network (UHN), where the follow-up clinics were held, approval was received quickly – just a few days after the second consent form was submitted. When speaking with the coordinator responsible for our protocol, she said “Oh, it’s a SARS protocol, it will be approved quickly”. For the third time, I felt a sense of tension. On the one hand, I was delighted that we would be able to begin the study quickly and on the other hand I wondered if there were ethical problems that the study team had missed and that the REB might also miss with a quick review. While I felt that our study was not risky, I wondered about other studies and how much risk these might pose and how all the SARS protocols could be evaluated so quickly.

9.131 Multi-Centre Reviews

The SARS outcomes study recruited survivors from hospitals across the greater Toronto area. This necessitated an REB submission and approval from each of the twenty-two recruiting institutions. Each site required its own consent form. Many requests for changes (both large and small) were made by the reviewing REBs; this was the most frequent reason for an REB to delay approval. Implementing the requested changes and tracking each of the forms took many hours of staff time and was viewed as particularly wasteful by CSRN staff. In the end, each consent form was unique, which to some extent negated the CSRN’s effort to maintain consistency across sites. Ironically, while a consent form was prepared and approved for each site, many of them were never used. Once the follow-up clinic at UHN became operational, patient contact occurred there and only the UHN forms were used. The twenty-second approval was obtained in May 2004, almost one year after the first submissions were made.
9.14 Obtaining Funding

The funding process was the fourth logistical challenge encountered during the SARS outcomes study. Few funding sources were available because the outbreak was not a predicable event and progressed rapidly. When funding was available, submission deadlines were short and awarding of funds was much quicker than usual. Within weeks of the beginning of the outbreak, the Canadian Institutes for Health Research’s (CIHR) Institute of Infection and Immunity obtained the necessary internal approvals, allocated funds to SARS research and issued a request for proposals for research relating to SARS. Protocols were submitted, peer review took place, and funds dispersed to the top ranked projects using normal processes in about six weeks. Thus the procedures used were those that are well established, but the timeline was accelerated. As a result of the special competition, $1,656,000 was awarded to four research groups across the country. Despite receiving a small grant from the Ontario Thoracic Society (OTS) and a very small amount from CIHR, the SARS outcomes study group did not have the funds to complete the study (the study received 3% of the total awarded to the CSRN by CIHR). Most of the funding was shifted from other internal sources to complete the project. I wondered if it was right to shift researcher priorities away from projects that had been peer reviewed and funded to this one that had not been peer reviewed, but that felt more important in the context of the public emergency.

9.2 Implementation of the SARS Outcome Study

The second stage of the study involved identifying and contacting potential participants, recruiting them to the study and then carrying out study procedures with survivors who agreed to
participate. The study protocol involved following patients for one year after their acute illness and was completed in November 2004, just eighteen months after the last patient in Toronto fell ill, a timeline that is much quicker than what is normally seen in this type of study.

9.21 Identifying and Contacting Potential Participants

The fifth time that things ‘didn’t feel quite right’ was during the process of identifying potential participants. Hospitals and public health units were bound by local, provincial and federal laws and guidelines to protect the privacy and confidentiality of SARS patients. However, in order to discuss the study with patients and thus allow them to choose if they wanted to take part in the outcomes study, the research team required SARS patients’ contact information.

Hospitals and infectious disease specialists reported names and contact information of every person affected with SARS to the public health units in the Greater Toronto Area (GTA). Therefore, these units might have been a good and complete source of contact information for our study purposes. However, public health units in the Toronto area were reluctant to release identifying information of people whose names they had acquired for surveillance purposes. They wanted to protect the confidentiality of the patients’ information. (Personal communication with a Medical Officer of Health, 2006) The sensitivity of information about some other diseases that are reportable (in particular sexually transmitted diseases) may reinforce this need to respect confidentiality. From our work with the outcomes study, we know that SARS was a highly stigmatized illness with patients at times shunned by their families, friends, neighbours and co-workers. Because public health personnel did not have the time to contact patients themselves to ascertain if they were willing to speak with research staff and study personnel did not have a
working relationship with public health units, we turned to the hospitals and clinicians, to obtain the names and phone numbers of SARS survivors.

Some of the contact information took months to receive from the institution where the patient had been hospitalized during their acute illness. The last list was received in June 2004 i.e., 11 months after the outbreak was declared over in July 2003, making this the most challenging logistical hurdle of the study. We were still calling people for the first time almost one year after they were discharged from hospital. Normally when new patients are recruited to a study, it is only within a narrow window of their acute illness, and the starting point of each patient in the study is staggered over months or years. Because SARS patients all fell ill within a short time span, this was not possible with this study, and it contributed to our unusual pattern of recruitment where the number of patients enrolled increased with each subsequent visit.

Each hospital was asked to prepare a list of affected patients and their contact information. Sometimes the generation of this list was facilitated through medical records and sometimes it was coordinated through a physician or nurse practitioner’s office. Because of the disarray caused by the restrictions in place during SARS, these lists were very hard to acquire. In total we received 198 names of the 307 adults who had survived SARS in the GTA. The varied reasons we did not receive all of the names remain unclear. Likely, the reasons were multi-factorial. There were three hospitals that did not send us any patient information. Many of the lists that we received were not complete. It is possible that the patients who were not listed had already indicated in some way that they were not interested in being contacted for any research, but we could not confirm this. Had there been more time and money to organize the study and had we been allowed entry into other hospitals, we would likely have recruited a research coordinator in each institution to approach patients about becoming part of the study. This was
not possible because of the timeline of the outbreak and because of infection control measures that were in place.

In order to inform SARS survivors that they were being referred to a research clinic, a letter was sent to the patients from the hospital where they had been treated for SARS. This letter, usually signed by the physician who had treated them while they were in-patients, informed patients that the SARS outcomes study was taking place and that a research coordinator would be calling them to inquire if they would like to participate. One SARS survivor at an outlying hospital was incensed by this process and called her local REB to complain saying that the hospital had no right to give her name and phone number to some unknown researcher downtown. All SARS survivors, however did not feel this way and several times over the course of the study, a participant asked us if we would agree to see her friend or co-worker who had not been on the list or approached originally for the study. We always agreed to see him/her. This self-referral to a research study is unusual, and demonstrates the range of patient reactions to our study, with some SARS survivors feeling it was so valuable that they wanted their friends to be able to participate and others wanting no part of it.

Throughout the recruitment period, I felt that because of public health’s desire to protect SARS survivors from researchers (personal communication from a medical officer of health), some patients were not given the opportunity to decide if they wanted the follow-up that the research clinic could provide. I was frustrated that we could not speak to all adult survivors at least once. Most of the survivors who participated felt that we offered them something of value. I wondered why confidentiality concerns were so strong in this context, and if there wasn’t something about the public emergency that might override them. I not only wanted to ensure that
we had an unbiased sample, I also wanted to offer the project to as many SARS survivors as possible.

9.22 Recruiting Participants to the Study

Recruitment to the outcomes study was also different from the process in my previous outcomes work. This was done after patients were discharged from acute care, and as a result some of the patients were unreachable. For 15 SARS survivors, there was incorrect phone information or we were never able to make contact with them despite multiple attempts (this was a very labour intense process – about 20-30 calls were required in some cases to find hard to reach patients). An additional 58 survivors declined consent. I was surprised by this high number of refusals based on my work with other studies. Some patients told us that they needed to put the whole situation behind them, and had no wish to enter a hospital; others said that they had been forced to take a lot of time off work and could not afford further time away. While these patients were offered home or workplace visits, some still declined. In order to determine if skewing of the sample had occurred because of lack of complete enrollment, we conducted a statistical comparison of several important variables between the total population of Toronto SARS survivors and those of the sample. (Table 5.1) More patients in our study cohort were health care workers and had received systemic corticosteroids and fewer had at least one preexisting medical condition, but they were otherwise similar to the 307 adult survivors of SARS in Toronto.

9.23 Obtaining Informed Consent
The consent form is only one small part of the consent process. The communication by research personnel with patients to describe the protocol and to answer questions is perhaps the most critical step in the process to maximize patients’ understanding of what will occur and why.

When the protocol was written, the outbreak continued and we imagined needing protective equipment to interact with patients. We were also unclear about the period of infectivity and whether patients would also need these same precautions. Had the need for protective gear continued, we might unintentionally have spent less time with patients during the process of informed consent. Because of our discomfort about the potential for spending less time with patients, we incorporated several steps into our consent process. We first explained the study to patients over the phone to ask if they were interested in more information about the study. If they were, we proceeded to explain the study to them in detail and answered any questions that they had. We then sent out the information/consent forms so that patients had time to read them and consult with family members, friends, or physicians. In the end, however, we were not constrained in our consent process by the infection control measures since the first patients were seen at about the time that the outbreak was declared finished. By then, we knew that patients were no longer infectious. In order to give the patients as much time as they needed to think over their participation, we continued with the long phone call prior to booking the first appointment and also continued to send out the consent forms ahead of time. Once patients arrived in the clinic, there was time for them to ask as many questions as they wished, although most did not require extra time. As will be explored in the next chapter, interaction with prospective study participants is the single most effective means to increase patient understanding about a research protocol and we wanted to maximize this interaction.
9.24 Carrying Out the Study Procedures

During the conduct of the SARS outcomes study, we were strained for resources, in particular personnel (physicians, coordinators/nurses and clerical staff) and clinic space. The number of long visits taxed our clinic infrastructure. During the period of frequent SARS clinics (July 11/03-July 7/04), 289 SARS patient visits were conducted. Because of the multiple tests and questionnaires that were done, visits (particularly the first one) were often in excess of four hours. This was five or six times more hours per week than our scheduled clinic time and personnel hours. Thus, we had an extended period of about one year where we were stretched much beyond the capacity for which we were originally scheduled. Two additional physicians were recruited to help with the load and they generously donated their time. While a research nurse coordinator hired by the CSRN provided invaluable help with the clinics, we had no other extra clerical or research staff. While extra funding would have helped, skilled professionals are difficult to find and this was particularly so during the outbreak as some research workers were seconded to other areas of the hospital. Hiring of new staff would have been difficult as people working in other institutions were not permitted into our hospital. A longer outbreak would have made these challenges worse. More staff would have helped us to stick more rigidly to the protocol schedule of visits i.e. see people closer to the 3, 6 and 12 month dates and cut down on the variability in timing of the visits so as to obtain more accurate estimates in outcomes. Resource allocation during an outbreak can have important consequences and this aspect of pandemic planning will be explored in more detail in the following chapter.

9.3 Conclusion
This chapter highlights the challenges encountered as the SARS outcomes study was planned and implemented. These include: 1) writing the protocol with speed and little knowledge of the pathogen and the sequelae of the illness, 2) writing the consent forms before details of the protocol were finalized, 3) quick local REB approval and protracted multi-site REB approvals, 4) funding, 5) identifying and contacting potential participants, 6) recruiting potential participants from other hospitals, 7) obtaining informed consent from a vulnerable population, and 8) carrying out the study procedures. These issues have tended to be under-examined because they look procedural in nature, but in fact as one digs deeper, the ethical nature of these problems emerges. These issues are often challenging in the conduct of research, but were made more difficult because of the context of the outbreak in ways that are described in chapter 11, after I have described the methods used (chapter 10) in this analytic inquiry. The current chapter describing the ‘case’ of the SARS outcomes study sets up the discussion of the ethical issues embedded therein, which are addressed in the next chapters.
CHAPTER 10: ETHICAL ISSUES ENCOUNTERED: METHOD

The purpose of this chapter is to describe the methods used for the analytic reflection of the ethical issues encountered in the conduct of the SARS outcomes study described in part I.

My first step was to take the logistical challenges that ‘didn’t feel quite right’ and to understand the ethical implications of each. In order to do this, I started to read about the issues that are prominent in the general research ethics literature. Up to this point in my career, I had had little exposure to formal research ethics training, so I applied for and was accepted to the collaborative program at the Joint Centre for Bioethics. The first course that I took was one that focused on research ethics. I also audited a course about public health ethics. These two courses gave me a lens through which I could understand the changes that had taken place during the conduct of research carried out during the SARS outbreak. I continued to read and began to look for reference to the ethical issues described in research conducted during other public emergencies. I found very little, although there was some mention of the ethics of conducting research after severe trauma or violence. I continued to think about and analyze the links between the information that I was reading and my own experience with the SARS outcomes study. The ethical issues that I describe in this part of the thesis are those that I saw with general research ethics and public health ethics lenses. Chapter 11 is the result of this analysis.
CHAPTER 11: ETHICAL ISSUES ENCOUNTERED: RESULTS

This chapter discusses the ethical issues that were encountered in the SARS outcomes study. Each of the challenges that was identified in chapter 9 is mapped on to one or more ethical considerations. Many issues are discussed in the research ethics literature, however, only those that were encountered in the SARS outcomes study are discussed. These include: 1) scientific value and validity, 2) resource allocation, 3) respect for free and informed consent, which includes sections on vulnerable populations, overburdening research subjects, and social obligation to participate in research, 4) respect for privacy and confidentiality, and 5) respect for justice and inclusiveness. The chapter begins with a discussion of the Tri-Council Policy Statement (TCPS) that provides guidance about the ethical conduct for research involving humans in Canada. 61 Although a revised draft 2nd edition of the TCPS is now available for public consultation and contains a new section on research ethics review during public emergencies 16, I refer primarily to the earlier 1998 edition (with 2000, 2002 and 2005 amendments) as it was current at the time of the SARS outbreak.

11.1 Research Guidance in Canada

The Canadian document that guides the ethical conduct for research involving humans, the Tri-Council Policy Statement (TCPS): Ethical Conduct for Research involving Humans is silent on the processes of research conduct and of research ethics review during a public emergency, but does provide a framework which may guide the thinking about research and
research ethics review both during a public emergency and under normal circumstances. The TCPS was first published in 1998 by the three councils (or agencies) that provide federally sponsored research funding i.e., Canadian Institutes of Health Research (CIHR), the Natural Science and Engineering Research Council of Canada (NSERC) and the Social Sciences and Humanities Research Council of Canada (SSHRC). All institutions in Canada that receive funding from any of these agencies for research on human subjects must show compliance with the TCPS. The obligation to respect the TCPS has been expanded to all research in federally funded institutions through ‘memoranda of understanding’ between the funding agencies and the institutions. Many institutions have thus accepted to follow the TCPS for all research, federally funded or not. A revised draft 2\textsuperscript{nd} edition is now available for public consultation and includes some guidance on research ethics review during public emergencies. The experience with SARS in Toronto in 2003 prompted the Interagency Panel on Research Ethics (PRE), the federal body with stewardship responsibility for the evolution of the TCPS, to develop this new section about overseeing research during a public emergency for the revised draft 2\textsuperscript{nd} edition of the TCPS which is discussed below.

The Tri-Council Policy Statement articulates a unique and specific framework of ethical principles to help guide ethical conduct of research involving human subjects. It says:

“research involving human subjects is premised on a fundamental moral commitment to advancing human welfare, knowledge and understanding, and to examining cultural dynamics. . . . An ethic of research involving human subjects should include two essential components: 1) the selection and achievement of morally acceptable ends and 2) the morally acceptable means to those ends.”

The ethical framework is embodied in the following eight guiding principles that are “to evoke thoughtful actions” (section i.5):  

61
1) respect for human dignity  
2) respect for free and informed consent  
3) respect for vulnerable persons  
4) respect for privacy and confidentiality  
5) respect for justice and inclusiveness  
6) balancing harms and benefits  
7) minimizing harm  
8) maximizing benefit

These principles and the guidelines outlined in the TCPS “are designed to help both researchers and REBs, as a matter of sound ethical reasoning, to scrutinize the contexts and accommodate the needs of specialized research disciplines” 61. The principles may have to be balanced against each other in situations where they conflict. There is no explicit mention of public health or population emergencies in the 1998 Tri-Council Policy Statement, although many sections are generally relevant. Several of these, including respect for free and informed consent, respect for vulnerable persons, respect for privacy and confidentiality, and respect for justice and inclusiveness will be discussed further in the sections below.

11.11 Special Circumstances of a Public Emergency

As part of the revised draft 2nd edition of the TCPS, there is a new section that applies to research conducted during a public emergency. It emphasizes that:

“special attention and effort should be given to upholding the core principles of respect for persons, concern for welfare, and justice when reviewing the ethics of research to be conducted in such emergencies.” 16

It urges institutions to formulate emergency preparedness plans so that research ethics review continues during the emergency, states that any exceptions made be limited to the duration of a publicly declared emergency and that should researchers request exemptions to the principles and policies stated in the document, REBs should take special care in the consideration of these requests. The acceptability of occasionally using videoconferencing as an alternate to face-to-
face meetings has been addressed by PRE in response to queries received by the panel. The need for this alternate meeting style was recognized during the SARS outbreak.

11.2 Research Ethics Guidance during a Public Emergency from the Literature

The research ethics literature is nearly silent on any special consideration for conducting research during a public emergency. There are however, several publications from which to draw guidance that were designed to apply to non-emergency situations, but that are relevant to all research. Table 11.1 compares the ethical issues about research conducted during emergencies as described in several relevant publications. The first of these is a summary of criteria that must be met in the conduct of ethical clinical research and that was penned by Emanuel et al. after they evaluated multiple guidelines (including the TCPS), and international codes. They argued that in order to be ethical, research must have: 1) value 2) scientific validity 3) fair subject selection 4) favorable risk/benefit ratio 5) independent review 6) informed consent and 7) respect for enrolled subjects. No mention is made of any special circumstances under which these conditions would not apply and in fact, they say that: “they are meant to be universal, although their application will require adaptation to particular cultures, health conditions, and economic settings.” Therefore, it is assumed that these principles apply during an emergency as well as in normal times. However, the social value and the risk/benefit ratio would be assessed according to the prevailing conditions.

Three other bodies of work are relevant to research conducted during a public emergency. The first group of reports is two descriptions of problems encountered during a public emergency; one after the Oklahoma bombing and one during the SARS outbreak in Toronto. Quick describes the coordination of the research that was undertaken after the Oklahoma
bombing and the benefits of a collaboration that oversaw all research carried out about the bombing. All research protocols related to the bombing, its impact and its aftereffects were reviewed by the University of Oklahoma IRB (Institutional Review Board, the American equivalent to Research Ethics Boards). This allowed the IRB to think about whether subjects were overburdened with research projects and to encourage researchers with similar projects to collaborate, pool their data and approach subjects just once for participation in a single project. Muller et al. chose the perspective of the researcher to describe some logistical challenges that were encountered as they strove to implement a clinical trial of ribavirin during the SARS outbreak in Toronto. Neither of these authors describe any issues that should be evaluated by the REB/IRB differently during a public emergency and because neither publications explicitly mentions ethical principles, they are not included in Table 11.1.

The second relevant body of work was that carried out by Gershon and her colleagues who undertook a study of the evacuation of the World Trade Center (WTC) after the terrorist attack in 2001. They chose to highlight the perspective of the protection of the research participants. Many of the issues cited, e.g., timeliness of funding and IRB review, access to participants and coordination across studies and agencies are logistical in nature but as in the SARS outcomes study these have ethical implications. Fleischmann and Wood who are affiliated with Gershon’s group wrote about these ethical implications in the context of victims of terror such as “acutely ill trauma survivors, refugees and others who experienced extreme situations” and speak of them as they relate to the principles of autonomy, beneficence and justice. They recommend that when a public emergency occurs 1) the appropriate politician should declare that a serious emergency has occurred, 2) research proposals should be coordinated and reviewed by a specially convened IRB that would
“encourage collaboration among investigators to decrease redundancy of research and oversampling of those affected by the event and ensure that the local IRB has taken appropriate steps to protect the interests of the subjects . . . keeping the interests of the subjects of the research as the primary focus of concern.”

and 3) specific protection should be put in place for research subjects who are victims of terror.

These should include: informed consent, privacy and confidentiality, with special attention being paid to the fact that the media may already have breached potential research subjects’ privacy; explicit mechanisms for mental health assessment referrals as needed; training for the research team specific to interacting with victims of terror. A process should also be in place for the review of complaints and adverse events.

The third body of literature that is relevant to research conducted during a public emergency is that of trauma research. This literature is vast, but only recently have some authors and organizations started to examine the ethical issues involved in such research. In January 2003, the New York Academy of Medicine and the National Institute of Mental Health convened a symposium titled "Ethical Issues Pertaining to Research in the Aftermath of Disaster" where four key areas were examined and discussed: decisional capacity of potential participants, vulnerability of research subjects, risks and benefits of research participation, and informed consent.

As can be seen from Table 11.1, where the ethical issues discussed by several of these authors is compared to those identified in my study, there is much overlap in the examination of the issues involved. All groups discuss respect for free and informed consent and respect for enrolled subjects. Gershon also highlights the special challenges of writing a scientifically valid protocol, identifying and selecting potential participants in a way that is just, resource allocation and respect for privacy and confidentiality during a public emergency, as I do later in this chapter.
Protection of researchers was also identified by Gershon as being important and this is always a challenge in an outbreak situation, but was not a problem for the SARS outcomes study since our work began after the survivors were no longer contagious.
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11.3 Social and Scientific Value and Scientific Validity

The first step in the research process is to formulate a research question and to design a feasible study which will provide insight into the question posed. The protocol must have social and scientific value and scientific validity. The Nuremberg code says in the third point that “the experiment should be such as to yield fruitful results for the good of society, unprocurable by other methods or means of study, and not random and unnecessary in nature.” This is value. Emanuel et al. equate scientific validity with a “methodological rigourous manner” Value and validity are different concepts and both must be present to make a protocol ethical. It is possible to ask a socially valuable question but write a research proposal that is not valid. Various types of validity and generalizability are described below in more detail. It is also possible to write research protocols that are methodologically sound, but ask trivial or already resolved questions.

During a public emergency, researchers have to write research protocols quickly even though critical elements may be unknown. McGeer cites several design and logistical reasons why this is difficult. The design problems that she discusses include the fact that the research question may change over time as knowledge and experience with the problem increase (value), that it is difficult to include the correct patients when case definitions are non-specific (validity), and that lack of knowledge makes the selection of appropriate outcome measures difficult (validity). The logistical issues that she cites include investigators being too busy with other emergency work to devote enough time to the research, investigators and REB members infected and/or quarantined and safety of research staff. All of these issues detract from an investigator’s ability to write a thoughtful and relevant research protocol that is feasible under the circumstances, and these limitations may lead to the generation of uninterpretable data.
“Research that produces uninterpretable data is not just a waste of time and resources, it is unethical” 63. It has no value.

When writing a research protocol for implementation during a public emergency, investigators may make inferences about clinical scenarios that seem similar to the current one – like SARS being “just ARDS” 72. Often in these circumstances, there will be no time to pilot research protocols, and connections will be made about similarities and differences and protocols will be written using reasoning by analogy. Researchers need to decide whether the potential knowledge to be gained outweighs the uncertainties in risk because of limited background information.

Clearly defining the population of patients to be included in a study i.e., inclusion and exclusion criteria and enrolling only those patients is crucial to internal and external validity of a study. External validity or generalizability is an important concept in epidemiology and a study is deemed to be generalizable when: “it can produce unbiased inferences regarding a target population (beyond the subjects in the study)” 73. Most epidemiological studies recruit only a small portion of the target population with the goal to make inferences about the larger population. In order for study results to be generalizable, studies must be free of sampling bias (referred to by some authors as selection bias 74,75). Sampling bias is a systematic error in the estimation of the exposure caused by a sample that is unrepresentative of the target population. 74 In some public emergencies, this will not be a problem, but in the special case of an epidemic, it may not be clear which patients are ill with the disease in question and which have contracted something else. The relevant diagnostic test may be unavailable, too costly, not yet developed or refined enough for the current context, too lengthy for research inclusion purposes or laboratory facilities may simply be overwhelmed with the demand. This was the case during SARS, where
no diagnostic laboratory test was available in the early phases of the outbreak and later only 28
days after initial symptoms presented and little clinical experience with the disease had been
acquired. Even once the test became available, laboratories were overwhelmed with the demand
and the tests were not complete until many months after they were submitted to the lab. The
initial symptoms of SARS were similar to other infectious diseases such as pneumonia or
influenza which made it difficult to differentiate it from these other conditions. Because
researchers did not consider the follow-up carried out in the SARS outcomes study to be risky,
we felt that if some participants had acquired another disease, they could be followed and
dropped from the analysis portion of the study once the results came back from the lab.

11.4 Resource Allocation

A protocol that is feasible under normal circumstances may not be feasible during a
public emergency. Care must be taken not to diminish the scientific validity of a protocol
because of lack of resources. When a project is not feasible, resources that are allocated to it may
be wasted and opportunity cost may be high. The logistical issues cited by McGeer above
(investigators being too busy with other emergency work to devote enough time to the research,
quarantine of essential research personnel and the safety of research staff) all must be
considered and important resource allocation questions answered before the research is begun.
During a public emergency, time, personnel with the required expertise, and money are all in
short supply. These resources are always difficult to acquire, but they become even more so
during difficult times. During an outbreak, participants who meet the inclusion/exclusion criteria
may also be in short supply.
The scarce resources that are needed for research should be allocated according to a scheme that is backed by a set of principles that is developed prior to the emergency. A review of the differing schemes used to allocate resources and the principles that guide them has recently been carried out. These principles include treating people equally (lottery and first-come, first-served), prioritizing those who may benefit most from the service (sickest first or youngest first), the utilitarianism strategy of maximizing total benefits (through number of lives saved, number of life-years saved, or based on prognosis) or promoting and rewarding social usefulness. All of these strategies have been used with some success in such situations as allocation of transplantable organs, triage of scarce medical resources during wars, and pandemic planning for distribution of vaccines, antiviral medication and ICU beds. Each also has drawbacks and adoption of these strategies to research carried out during a public emergency is challenging. Developing these ideas ahead of time allows for thoughtful reflection on the issues and for consultation with various stakeholders. Once the emergency occurs, any contextual features that are thought to be relevant to the particular emergency can be incorporated into the scheme. Transparency, a value which was identified as important during the SARS outbreak, about how resources are to be allocated is key to this aspect of pandemic planning.

Researchers must decide whether to undertake research during a public emergency (and if so, what proportion of their time will be allocated to research) or whether their time and expertise would be more appropriately devoted to clinical care in these circumstances. One of the scarcest resources during an emergency is appropriately trained personnel. Once the decision is made to undertake research, it must be decided which research is essential. When many features about a pathogen or a disease process are unknown, it may be difficult to evaluate the potential scientific value of the completed project. To be methodologically acceptable, a research project must
evaluate the correct endpoints and be adequately powered to answer the study question. Resources might be better spent on pre-clinical studies to fill in the missing information if appropriate endpoints and/or the appropriate study sample cannot be identified. Researchers must weigh both the risk that these uncertainties have on the study design and also the risk to patients in proposed studies when these uncertainties are present against the potential value of the knowledge that might be gained from the research.

Recruitment for the outcomes study was logistically more challenging than in other outcomes studies on which I had worked. When recruitment problems are pronounced, the result may be a sample that is not representative of the total population. This may skew the study results in unknowable ways and result in a study that lacks external validity. When recruitment is so skewed that study results can not be generalized to any other population, this feasibility problem can become an ethical one if validity is not achieved. A study that is seen to be flawed in the number and/or type of patients that were recruited may waste resources, the time that researchers invest and patients donate, and is of little social value and has no scientific validity.

Even when the investigators of the study do not feel they have recruited a biased sample or one that is too small, journal editors may not agree and decline to publish the study and limit dissemination of study results. Another difficulty that we encountered as a result of our recruitment strategy was the fact that new participants joined the cohort at each of the three time points. This may have decreased the validity of our comparisons between the 3-, 6- and 12-month study variables, as the sample was different at each of the three time points. Thus the scientific value of our study may have been affected by these challenges to recruitment. However, in order to include as many patients as possible, we felt that this was the only fair way to proceed as describe below in the section on justice and inclusiveness.
In an outbreak situation, time is of the essence, but researchers still need to obtain REB approval for their protocols. Important research questions may not be answered if the research cannot proceed while the outbreak is in progress. Muller et al. describe how the outbreak moved across sites and by the time they received REB approval at one site, they had to begin the REB approval process again at a new site. As a result of these delays, valuable opportunities for the generation of new knowledge may have been lost. When REB approval is mired in long delays and inefficiencies during an outbreak, scarce resources may be wasted and opportunities for additional knowledge may be lost.

When a study is conducted at multiple sites and separate REB submissions are required for each site, the REB submission process may be onerous and waste research staff time unnecessarily. This was the case in our SARS outcome study where research ethics review was submitted to twenty-two REBs across the greater Toronto and Hamilton areas. The last approval was received fourteen months after the beginning of the outbreak. A central REB, recognized by all of the hospitals with researchers interested in conducting SARS projects, would have helped REBs across Toronto to carry out more unified and timely reviews of the SARS-related protocols. The structure of REB review in Toronto continues to be one where every hospital has its own REB (except for cancer trials).

11.41 Multi-Centre Reviews

The need to submit the same protocol to many different institutions was an inefficient use of scarce resources available for SARS research. From the point of view of an individual researcher, this inefficiency was mitigated in part, by the completion of the submissions by a central collaborative network of SARS researchers (Canadian SARS Research Network (CSRN)).
However, the submissions took months to prepare and receive approval which meant that researchers could not begin their studies at all sites at the same time. While some researchers may have found the wait frustrating, there was a silver lining since the delay at some sites helped to attenuate the need for surge capacity when all of the work did not begin at the same time.

A mechanism for ethical review that was recognized by all of the participating sites would have helped reduce the inefficiency involved in dealing with so many REBs. Perhaps research ethics review for all sites could have been coordinated through the university or the task force that was set up by the provincial government to deal with the outbreak. At the very least, REBs might have communicated with each other to better understand the concerns that were raised by those who had reviewed the protocols earlier. A single centralized system for REB approval, which was recognized by all affected hospitals, would have been very helpful in avoiding redundancies in the current system.

In order to be useful during a public emergency, such an REB would have to be operating in such a way that, once the emergency was declared, it could immediately switch its focus to the emergency protocols. Thus, there would need to be either surge capacity to deal with these extra protocols or a mechanism to triage protocols so that the most urgent emergency-related protocols could be intermingled with the work that had been previously planned for the REB. Local feasibility issues might be particularly challenging to assess in this context and local representation of the REB would be crucial to deal with this. Further discussion about multi-centre review is undertaken in section 14.5.

11.42 Feasibility & Surge Capacity
When the required infrastructure and expertise are not already in place, it may not be possible to mount a research project quickly enough to proceed with outbreak research. Prior to the SARS outbreak, the research team I worked with had been conducting a five-year outcomes study of Acute Respiratory Distress Syndrome (ARDS) survivors. 53 We had a team in place that worked well together and was knowledgeable about the procedures necessary to ensure that subjects were retained in the cohort 79 and to successfully support a follow-up study. Without the expertise gained from this previous work and the infrastructure that was in place, the SARS outcomes study would not have been feasible. However, our team was small and we struggled with surge capacity, which is closely related to feasibility.

Our ability to handle the surge of lengthy clinic appointments was helped by the fact that visits were only loosely clustered around the target dates. Clinic staff strove to respect patient’s schedules. In a more rigid study design, this might have undermined study validity. However, we knew the reality of following survivors of an acute illness, especially as they re-integrate into the community and into the work force. If researchers try to impose rigid patterns of clinic attendance, subject retention may be compromised. 79 Thus surge capacity is an important component of feasibility of a research protocol conducted during an outbreak. When surge capacity is not available in the study infrastructure, the value of a smaller study must be evaluated by the research team in the context of the outbreak.

Surge capacity refers not only to the need for physical spaces, but also to a need for skilled personnel to complete the required tasks. 80 However, this is difficult to anticipate in the research context as funds are always limited. It is a resource allocation issue. Unless research protocols are written ahead of time, it is difficult to foresee where the surge capacity will be needed. Most of the capacity issues that we faced in the SARS outcomes study would have been
helped by additional personnel who were skilled in communication with patients, discussing the
study with them, obtaining informed consent and organizing the clinics. These are fairly generic
skills that are commonly held by research nurses and coordinators. A pool of such personnel,
deemed to be nonessential during the emergency and therefore available to be seconded, could be
organized to meet these potential needs, if these staff members are not needed for clinical care.
The longitudinal nature of the outcomes study made the need for extra personnel more acute
since it extended beyond the emergency itself.

Recruitment difficulties, feasibility of the protocol, and the availability of surge capacity
may all affect the scientific validity and social value of the research and, if compromised, could
render the project unethical. 63

11.43 Funding

Few funding sources were able to meet the timelines resulting from the rapid spread of the
SARS virus. CIHR was able to accelerate its processes and funds were awarded quickly.
Although they put out a special request for research proposals, the procedures followed
(competition for funds and peer review) were similar to those usually employed for award of
research funds. Another mechanism should be developed that would be more amenable to
funding research during a public emergency in a timely fashion, perhaps one that emphasizes
collaboration more than competition. Weiss comments as she discusses the laboratory
collaborative efforts that occurred:

“This combined effort would not have been possible if the investigators had
waited to receive specific funds to tackle SARS; rather, they diverted influenza
funding urgently to explore this new emergency. Moreover, they could not have
made such excellent progress if there had not been a pre-existing network of
influenza surveillance and reference laboratories, and a rapid and open means of
exchange of information and materials between them, and above all, a sense of trust and mutual endeavour.”

I have found no details about how funding was handled in other public emergencies in North America. Several sources of monies are available (for a list of these, see Cox) in the United States for disaster research, but most require that protocols be submitted and approved in advance; I am unaware of similar sources in Canada. In the report of the research structure that evolved following the bombing in Oklahoma City, several studies were discontinued due to lack of funds. Some successful researchers both during the SARS outbreak and following the Oklahoma City bombing were able to piggyback the disaster research onto existing, but relevant grants that were already in place.

I have several questions, but no answers about the funding of research in the context of an outbreak. Is the standard competitive format the best model to follow when an agency wants to allocate monies for research during an outbreak, or is there a method available that would foster a more collaborative effort? Is there a funding mechanism that could foster new working groups that are small enough to be functional, but large enough to allow for collaboration across various specialties? How can front-line professionals be more involved in the research when they have no time to put together research protocols? Is involvement of front-line workers possible without exposing more people to the risk of infection?

Time, personnel with the required expertise, and money are always in short supply, but these shortages may be felt more acutely during a public emergency. Similarly, multi-centre review, feasibility, surge capacity, and funding, which all have aspects of resource allocation, may become more important, but also more challenging than usual during a public emergency.
11.5 Respect for Free and Informed Consent

Respect for a research subject’s autonomy is a cornerstone in research ethics in North America and has been emphasized in international codes since the Nuremberg trials. \(^{63,70,83,84}\) In order to show this respect for a patient’s autonomy, there must be a process that allows for a free and informed choice to be made by the potential research subject. \(^{61}\)

This sub-heading is divided into four sections. In the first (11.51), I discuss the process of obtaining free and informed consent. Part of this process is the form that is used to document that the process has occurred and this is the focus of the second section (11.52). Section 11.53 discusses respect for vulnerable populations, including overburdening research subjects and in section 11.54, I review the literature on the social obligation that may be felt by research participants.

11.51 The Consent Process

The process involves disclosure, comprehension, voluntariness, competence and a decision about participation in the research. \(^{85}\) The three conditions required for the process to be free and informed consent are 1) autonomous action or intentionality (willed in accordance of a plan); 2) understanding and appreciation (competency, a key element of the this condition is also discussed below); and 3) voluntariness. \(^{85}\) All of these steps are important, although the degree to which each is required has been discussed by several authors \(^{86-88}\) and each may be affected by the circumstances of the public emergency.

Disclosure of information to research subjects involves the informed consent form, the consent process and any other supplementary mechanism such as a video or interactive web site. In a public emergency, there is time to write a familiar form for which we may have an
institutional template, but supplements are likely not feasible unless the protocol was written ahead of time. Disclosure must be made in such a way as to be understood by the potential participants, and may be affected by infection control measures such as gowns and masks which interfere with non-verbal communication and policies of reduced interaction with participants which may discourage questions about the research. In normal circumstances, a form that is short and to the point \(^8^9\) is more likely to be understood, and this may be even more important when a stressful situation is present such as a public emergency.

Some authors have questioned whether victims of a traumatic event are competent to make the decision about participation in a research project. \(^9^0,9^1\) The same questions may apply to research participation during a public emergency. Rosenstein delineates the decision making continuum as follows: unable to make decisions, able to assign a substitute decision maker, able to make medical decisions, appreciates the difference between clinical care and clinical research and finally able to make all decisions in this context. \(^9^0\) Most victims of a disaster will have been fully competent prior to the trauma and it may be inaccurate and stigmatizing to classify this group of individuals as unable to make decisions after the event. Several factors such as degree of injury, locale and type of the inquiry and time since the event will influence decision making capacity. \(^9^0\) Nothing is known about whether the same is true of victims of an infectious disease outbreak, although most of these victims will also have been fully competent prior to their illness. Competency is decision specific and influenced by many factors. It is possible that such factors as media attention, worry about spreading the illness to family and friends, and inability to effectively communicate with family and other social support systems because of quarantine and isolation, all of which were present during the SARS outbreak, may influence decision making capacity to participate in a research project.
Ability to make an informed decision about participation in a research project may also be more complicated when potential subjects are seriously ill as they were during the SARS outbreak.

While critically ill patients are routinely involved in research projects in an intensive care setting, factors surrounding the public emergency (such as quarantine, isolation, disallowing visitors into the hospital and uncertain risks about the research) may make it more difficult than usual to make informed decisions. Decisions about whom to approach about enrolling in a research project must be made by study personnel. It is not known if any extra precautions are needed because of the emergency situation and if the process should be different than similar decisions about approaching patients with other diseases in normal times. Instigators must put a mechanism in place to evaluate capacity if there is concern that many of the potential subjects are incapable of making a decision about participation in the proposed research.

Voluntariness \(^{85}\) spans a continuum from 1) coercion, which can have a completely controlling influence, 2) manipulation which has a large range of influence and 3) persuasion which can have a completely non-controlling influence and is compatible with substantially autonomous acts. \(^{85}\) It is unknown if voluntariness is affected by aspects of a public health emergency such as peer pressure to help learn the utmost about the health problem of concern. Peer pressure to join in the research effort may be heightened when groups of people who work together are affected e.g. the many health care workers at the two epicentres of disease in Toronto.

The informed consent process also depends on research staff being able to convey the necessary information to potential participants. For SARS studies that were conducted earlier in the outbreak than the SARS outcomes study, infection control measures may have interfered significantly with information giving aspect of this process. Face-to-face meetings were kept to a
minimum and when they occurred, the staff member who was conducting the informed consent process was in protective equipment that cut down on nonverbal communication. This may have affected how information was conveyed to participants of research protocols and consciously or unconsciously cut down on the amount of time that research personnel were willing to spend with potential subjects. One source, albeit fictionalized, estimates that a SARS patient received just seven minutes per day in direct contact with the health care team. 92 Patients were encouraged to phone the nursing station when they had a question or needed something. 92

11.52 The Consent Form

The consent form must accurately reflect the study protocol and what is required of patients. The form itself is an evidentiary document which symbolizes the importance of the process and shows that researchers are mindful of a potential research participant’s autonomy. However, researchers struggle to write consent documents that patients can understand. 93-98 A recent systematic review of strategies to increase patients’ understanding of the study for which they are being approached found forty-two articles that used multimedia or other forms of enhanced consent processes and concluded that the most effective strategy to increase comprehension and retention of the information presented is to have a study team member spend time talking one-on-one with the potential participant. 60 Perhaps as Arge et al. comment, we should be providing only the simple facts in the consent document, and have this backed up with information that patients could take home with them and consult as they need. 99 Articles about improving both the consent form and the consent process continue to appear and reflect researchers’ and REBs concern that we do not yet fully understand how to provide materials to maximize understanding and retention in our patients. 93-95,100-102 Having said this, Sreenivasan
argues that while investigators should take reasonable steps during this process to ensure that the patient understands the risks of the proposed research, there is a limit to what is required of researchers and “the minimum standard cannot simply be whatever it takes to produce comprehension” 86,87

As described above, participants in the SARS outcomes study were asked to sign two consent forms. The first described the SARS outbreak in general, outlined the overarching objectives of the CSRN and the rationale for many of the blood draws that were done. The second one provided more detail about the follow-up portion of the study. (Appendix I) Multiple consent forms for different portions of the same protocol are not uncommon. Care should be taken so that the new information contained in the second form is placed in the context of the previously given information and that the second form is relatively short. Assessing the number of consent forms needed is challenging when the information is complex and when, as was the case for the CSRN consent, the information is novel and evolving. When patients are overwhelmed with paper work, the risk is that they will not read the documents thoroughly. If it appears that investigators are not giving patients accurate details of the study commitment, this may reflect badly on investigators. Enrollment may be compromised if patients feel that the consent process is not optimal. 60 If patients feel that they have been misinformed about a research project in which they enrolled (when for instance they have not fully read the details of participation), it may act as a disincentive for enrollment into future research projects. 60

11.53 Respect for Vulnerable populations
Respect for vulnerable populations is one of the guiding principles in the TCPS. The TCPS describes who these vulnerable groups might be and states that special procedures may be required without specifying what these special procedures might be:

“Respect for human dignity entails high ethical obligations toward vulnerable persons – to those whose diminished competence and/or decision making capacity make them vulnerable. Children, institutionalized persons or others who are vulnerable are entitled, on grounds of human dignity, caring, solidarity and fairness, to special protection against abuse, exploitation or discrimination. Ethical obligations to vulnerable individuals will often translate into special procedures to protect their interests.” 61

The revised draft 2nd edition of the TCPS specifically mentions that new groups may become ‘vulnerable’ during an emergency and that:

“REBs and researchers should be aware that individuals, potential participants, researchers, and institutions that may not normally be considered vulnerable may become so by the very nature of public emergencies. Those already vulnerable may become acutely so. REBs and researchers should ensure appropriate evaluation of the risks and potential benefits posed by any proposed research, including provisions for greater-than-normal attention to risk, where applicable.” 16

The term vulnerability has been applied to many populations so that everyone in some circumstance might qualify. 103,104 This over-inclusiveness has the potential to render the term meaningless. 103 While exclusion of vulnerable populations may serve to decrease the number of individuals that a researcher may recruit to a study, a fundamental requirement of science demands that investigators seek to enroll as many patients as necessary to adequately answer the research question that has been posed. 63 As discussed above, investigators should ensure that decision making capacity is assessed by a qualified individual if there is concern that it will be impaired in many of the potential subjects. 90 Rather than apply the term ‘vulnerable’ to potential research populations in a public health emergency, researchers may be better served to ask the series of questions suggested by Levine in order to assess areas where care should be taken to
protect patients. The discussion of the term vulnerable in several research contexts (biomedical, social science and mental health research) and concludes with a section about vulnerability in the context of disaster research review. The questions she suggests include asking about whether there is political or social turmoil that might affect participants' ability to make an informed choice and whether upsetting or traumatic interviews have already taken place such as by the police or news media (or as in the case of the SARS outbreak, by public health officials). She also suggests that procedures be put in place to (1) provide assistance to those who experience difficulty during the research period and (2) to inform the participants of the results of the study.

Relatively little is known about whether potential research subjects feel vulnerable during a public emergency. What we do know comes primarily from research carried out after traumatic injury. Newman et al. reviewed the literature about how subjects feel after participating in traumatic stress research and conclude that the majority of patients do not regret agreeing to be questioned nor do they feel harmed by the research. In fact, several studies note that the experience can be a positive one. However, all authors report a minority of patients (ranging from 2% to 25%) who report distress as a result of participation. Boscarino et al., reporting on people studied after the attack on the World Trade Center (WTC), provide evidence supporting the relatively modest adverse impact that participating in a study about a public emergency has on respondents. Only 15% of residents from New York City that were surveyed reported that some of the interview questions were upsetting. While it is not known what an appropriate threshold for being upset should be, nor is it known what proportion of people are upset by questionnaires not related to traumatic events. Fewer than 2% were still upset at the end.
of the survey. In addition, a large majority felt positive about participation. Newman et al. conclude by saying:

“Avoidance of trauma assessment and research furthers the belief that a trauma is something that should be stigmatized and silenced. Providing the opportunity to participate in trauma research, along with appropriate information regarding costs and benefits, may empower trauma survivors by promoting autonomy.”

I agree with this statement and suggest that the same is true about research during a public emergency. Thus we may have empirical evidence about how subjects feel about participating in research after a traumatic event. While vulnerability may exist regardless of how people feel or what they say in surveys, being part of a vulnerable group does not preclude being part of a research project and we may be able to generalize these data to the vulnerabilities of those who participate in a project after a public health emergency. There are, however, important differences, particularly when the emergency is the result of an infectious disease. The most notable of these, is that some of the research during an outbreak may take place during, rather than after, the emergency and we do not know how subjects react to this timing. Also, the trauma research was primarily interviews and surveys about the event. We know little about how people feel about participating in the development of a diagnostic test, genetic testing about susceptibility to a virus or a randomized drug trial during an outbreak of an infectious disease. Thus, participants in research about a public health emergency may not feel vulnerable but care must be taken when generalizing the results from traumatic stress research to another context i.e., an infectious disease outbreak or any other public emergency. Researchers should ensure that psychiatric or psychological counseling is available to subjects who feel distressed about participating in research during a public emergency, even if the number of people who need the service is small.
11.531 Overburdening Research Subjects

Levine also suggests that REBs ask whether the population is at risk of being asked to participate in more than one study. The notion of too many studies overburdening research subjects is mentioned by Fleischman and Wood and by Quick but appears to be backed by little empirical data. A question about eligibility to multiple studies is also included on the Toronto Academic Health Sciences Network (TAHSN) research application so it is possible that the idea of patients being overburdened by being asked to participate in several studies may be quite pervasive in the thinking of researchers and reviewers despite the lack of evidence. The United States Office for Human Research Protections (OHRP) guidelines for institutional review boards (IRBs, the American equivalent of the Canadian REB) talk about not overburdening subjects, but also caution researchers not to be paternalistic i.e., to allow potential participants to make up their own minds about participation. These guidelines do not specify that presenting multiple protocols to patients is over burdensome.

During the SARS outbreak, there was a relatively small pool of patients to draw from (387 falling ill and 307 surviving adults) although impact studies were often looking at issues involving more people e.g., all health care workers. Some subjects enrolled in the SARS outcomes study told the research team that they were overwhelmed with and confused by requests to participate in research. Others offered that they would like to be included in as much research as they could. The question of how overburdened potential subjects feel and what is the ‘right’ number of studies to be approached about is an area that is understudied. Further empirical research needs to be undertaken to elucidate these issues. Researchers need to be cognizant of the number and type of studies proposed by the research community as a whole, which means that there must be some communication between research groups. A central registry listing all
emergency-related research and a determination of priority of protocols by a central REB would also help researchers decide who should be approached and when. Ethics boards should also be aware of trials which are mutually exclusive and which are competing for patients. Perhaps as Gordon suggests, potential participants ought to be told about all of the ongoing trials, their risks and benefits and the decision to join be left to the patient. This could be facilitated by a single REB for the emergency, as was the case after the Oklahoma bombing.

11.54 Social Obligation to Participate in Research

There has been discussion in the literature about patients’ social obligation to participate in research projects. Caplan says that health and knowledge are viewed as public goods that accrue to all members of society. In order to generate these goods, public participation is required. Caplan references Jonas and Fried, writing separately, who note that health and knowledge are not always readily available to all members of society and thus they may not be public goods. The nature of the research that we are encouraged to participate in here is not clear and could perhaps generate a never-ending obligation. Jonas argues that the need to respect autonomy is a much stronger force in our society than the need to create public goods. The obligation to respect one’s individual rights is concrete and enforceable. Despite these differences, these values appear to clash. Even if one agrees that health and knowledge are public goods, there is no clear duty of citizens to improve these public goods. Jonas does, however, argue that a duty to participate in research may be generated on the grounds of a social contract. We can presume the existence of a tacit contract, he says, by those who accept the benefits of knowledge and health, and thus these individuals have incurred an obligation of reciprocity to past generations that made the knowledge possible. In this argument, patients must participate in
research so that future generations may similarly reap the benefits of new knowledge. Harris argues that the obligation to participate in research comes from the free rider argument which is based in fairness to others. We all benefit from the advances made in medical sciences, including the need for and access to clean water, decrease in infant mortality, recognition of the need for good nutrition and the discovery of antibiotics. Others have contributed to these advances, and “since we accept these benefits, we have an obligation in justice to contribute to the social practice which produces them.” Evans takes the responsibility a step further and asks whether patients should be allowed to veto their participation in clinical research. He likens research participation to payment of income tax which few of us like but that grudgingly most of us comply with. Brassington, while seemingly not disagreeing with the duty to participate in research takes issue with the reasons that Harris claims underlie this obligation.

A lively discussion has ensued, with Chan and Harris rebutting Brassington’s argument, and Perna taking issue with Evan’s point of view. Schaefer, Emanuel and Wertheimer have also joined the discussion and recommend that:

“There needs to be a cultural shift in the moral framework that is brought to participation in research. The standard view of research participation must be changed from one in which participation is supererogatory to one in which individuals need to give a good reason not to participate. The shift should be from participation in biomedical research being, like charity, above the call of duty, to such participation being a moral obligation for everyone to do his or her part.”

Thus we have important philosophical discussions on this possible social obligation to participate in research, but no clear direction. Certainly all international codes of research ethics advocate the need for informed consent and currently the principle of autonomy appears to dominate any moral obligation on a subject’s part to participate in research.
These thoughts apply to normal times, but duties may be different in an infectious disease outbreak. Jonas tells us that:

“The physician who desperately battles a raging epidemic is under a unique dispensation that suspends in a nonspecifiable way some of the strictures of normal practice, including possibly those against experimental liberties with his patients. No rules can be devised for the waiving of rules in extremities.”

Thus while arguing, as mentioned above, that the need to respect autonomy is a strong force in our society, he recognizes that a pandemic situation is different. In that case, when there is a potentially dire threat to society, one can ask more of people. Under these special circumstances, perhaps the need to take into consideration vulnerabilities diminishes.

During the SARS outcomes study, some patients did speak of the fact that they felt that they ‘should’ participate in as much research about the disease as possible. Others however, felt that they had suffered enough by becoming infected and that they could not participate in any research projects. Thus, I think even if one believes that a moral obligation to participate in research exists or that the rights of an individual in this matter may be suspended in the context of an outbreak, not enough is known about the special vulnerabilities that having a stigmatizing, socially-isolating infectious disease involves, to know how to enforce this moral obligation to participate in research or to understand the harms that could result.

11.6 Respect for Privacy and Confidentiality

The rights to privacy and confidentiality must be respected in every research project. The right to privacy is entrenched in the Canadian Charter of Rights and is one of the guiding principles of the TCPS which says that in the research context: “the standards of privacy and confidentiality protect the access, control and dissemination of personal information.” Privacy
is vested in the patient. Battin et al. speak of lack of privacy as being about something very close to the person: “invasions of the body, personal space or liberty”. Some SARS patients would have preferred to maintain complete privacy and not have SARS outcomes study personnel call them to explain the study – they wanted to be left alone. Confidentiality is generally more relevant in the case of patient care. It is a duty that is owed by a health care provider to a patient. Confidentiality refers to “the ethical principle or legal right that a physician or other health professional will hold secret all information relating to a patient, unless the patient gives consent permitting disclosure.” Information about a patient’s health should not be released to unauthorized persons. Because in the context of research there may not be direct benefit to research participants, it is even more important to safeguard the patient’s confidentiality than when providing clinical care where benefit is assumed. Having made the distinction between confidentiality and privacy, however, this distinction has been muddied somewhat with so-called ‘privacy legislation’ that is about the transmission of information of all types – financial, health and social data. “Infectious diseases provide many good examples where confidentially matters more than privacy”. One thinks of the stigma attached to having leprosy, tuberculosis (particularly XDRTB) or AIDS. Once this type of diagnosis becomes known to insurers, employers or landlords, there can be dire consequences to the patient. The rest of this discussion is about confidentiality of personal and health information.

As Levine states in her preamble to the Guidelines on AIDS research, confidentiality is a complex issue made more complex in the context of an epidemic. It is an important consideration in all research, but the special case of the vulnerability of epidemic victims draws this to the forefront in a way that we have not seen since the AIDS epidemic began. Early in the AIDS epidemic, the HIV/AIDS community was very worried about harm that might ensue should
confidential information that affected individuals had shared for research or surveillance purposes be disseminated to government agencies, landlords and others. ¹³³

Public health officials wanted to protect the confidentially of SARS survivors (personal communication) and were reluctant to share their contact information with the SARS outcomes study personnel. This level of concern was not something that I had encountered before. This was particularly evident in the fact that we knew the names of some SARS survivors from articles in the popular press, and yet could not recruit these people. The media and the medical profession have a different set of rules about confidentiality. Sharing information between an institution that houses information and a researcher in another institution that would like to contact the patient is not something that we know how to do well. This is particularly so when these institutions are part of different systems as are hospitals and public health units in Ontario. The public health system and the individual hospitals had the contact information of all SARS patients, while academic researchers needed these data to discuss with patients if they wanted to be part of the SARS outcomes study. Not only is it necessary to protect the confidentially of subjects who decide to participate in the research, we must also protect those who choose not to. ²¾ Zwi comments that this is even more important in circumstances of turmoil and when there may be pressure from authorities for citizens to be part of research protocols ¹³⁴ as might be the case in a public emergency. Ideally, a researcher within the public health system who was collaborating with the CSRN would have contacted all patients, explained all aspects of the study to the patient and asked if they were interested in proceeding. In this way, the information could have remained housed in the system that had a relationship with the patient until the patient gave permission for his/her information to be released to the academic researchers. The process of placing a study-affiliated staff person in the institution that housed the information would have
maintained the confidentiality of all survivors whether or not they chose to participate in the research project.

Public health units are mandated by provincial legislation (in Ontario, the Health Protection and Promotion Act (HPPA)) to collect surveillance data for a long list of reportable diseases and SARS was added to this list during the outbreak. In Canada, public health units are not affiliated with hospitals, although there may be a public health official in some larger hospitals to facilitate reporting of these diseases. The most common reasons cited for the need for accurate and complete reporting are 1) to detect outbreaks and epidemics, 2) to enable timely follow-up of communicable disease reports so that further transmission is prevented, and 3) to facilitate the prompt implementation of appropriate public health interventions and educational efforts. However, the regulations regarding use of the information collected does not discuss the special case of an outbreak of a novel pathogen nor do they offer guidance about use of information for research purposes in this context particularly when the research is conducted in an institution other than the public health department.

While public health officials wanted to protect the confidentiality of SARS survivors, this value was in conflict with the goals of the SARS outcomes study. Study personnel wanted to distribute the potential benefits of participation in the study as widely as possible, so that each SARS survivor received his/her fair share, a form of distributive justice. From the point of view of study personnel, it appeared as if the principle of confidentiality and the principle of distributive justice (to allow all SARS survivors the option to decide if they wanted to be included in the study as described below) were in conflict with one another. However, I soon realized that this part of the story may not really be about principles. It is as much about the
interface between public health and research and questions about the mandate of public health and its impact on research.

Health privacy legislation was enacted shortly after the SARS outbreak in Ontario. Had the legislation been in place prior to SARS, the regulations would have been clearer, but the difficulties that were encountered in the SARS outcomes study may have been more challenging. How privacy legislation might affect research conducted during a public emergency has not been described.

Once patients were enrolled in the SARS outcomes study, research staff continued to do their utmost to protect survivors’ confidentiality. This was particularly challenging with patients who were also health care workers who might be known to colleagues who they met while attending the SARS outcomes study clinic. SARS survivors also worried about what might happen to their personal health insurance rates when it became known that they had had SARS. People who are self-employed such as physicians and some physiotherapists were particularly sensitive to the insurance issue. In the SARS outcomes study, there was at least one self-employed person who refused to either undergo a test or to accept a referral to a psychiatrist, for fear of insurance repercussions.

Researchers, hospitals and public health officials strove to maintain the confidentiality of SARS patients’ information. However, the operationalization of this aim sometimes led to disagreements and difficulty in achieving the goals of each group. The difficult interface between these groups was brought to light because of the need of each group to maintain the confidentiality of the data they had collected and is discussed further in Chapter 17.

11.7 Respect for Justice and Inclusiveness
The TCPS includes respect for justice and inclusiveness as one of the eight guiding principles. It says:

“Justice also concerns the distribution of benefits and burdens of research. On the one hand, distributive justice means that no segment of the population should be unfairly burdened with the harms of research. It thus imposed particular obligations toward individuals who are vulnerable and unable to protect their own interests, to ensure that they are not exploited for the advancement of knowledge ... On the other hand, distributive justice also imposed duties to neither neglect nor discriminate against individuals and groups who may benefit from advances in research.”

The principles of justice and inclusiveness must be respected through a fair selection of research participants. Emanuel et al. say that the selection of subjects must occur in a manner “that stigmatized and vulnerable individuals are not targeted for risky research and the rich and socially powerful not favored for potentially beneficial research.” Study personnel decided that the best way to do this for the SARS outcomes study was to approach every survivor in the Toronto area. We did not want to make arbitrary decisions about which patients are given the option to participate. By doing this, we would be respecting the principle of justice as well as respecting the autonomy of potential participants. However, respect for confidentiality required that health care institutions not give identifying information to those outside their own walls. At the same time, researchers were obligated to protect any populations that were deemed to be vulnerable. The principle of justice and the need to respect confidentiality had to be balanced against each other, keeping in mind the potential value of the proposed research.

The principle of justice is also invoked in discussions of resource allocation as discussed above. These discussions are usually about how to distribute a limited resource in an equitable fashion. Here we were dealing with a slightly different problem. We felt that we had a valuable service to offer to SARS survivors, albeit in the form of a research project. We wanted to reach
as many SARS survivors as possible yet we felt blocked by others concerned about the need to protect vulnerable populations and the confidentiality of their health information. We balanced the goal to include all patients who wanted to be part of the study with the scientific validity of the protocol and judged inclusiveness to be the more important value in this case.
CHAPTER 12: SUMMARY AND LINK TO PART III

Public emergencies, including pandemics, natural disasters and civil unrest often occur with little warning and may change the climate of research drastically. Some may say that we have no time for ethical niceties in these emergency situations, but it is precisely under these circumstances that we need them the most.

In the preceding chapter, the ethical challenges encountered in the conduct of the SARS outcomes study are described. Many of these challenges were the result of the short timeline available to the research community as it strove to learn as much as possible about SARS and its consequences.

During a public emergency, both social and scientific value and scientific validity of proposals must be maintained despite the need for protocols to be written quickly. Many variables, including appropriate outcomes, may be unknown and researchers may be forced to make analogies based on similar situations previously encountered. In order for the protocol to have generalizability (if the proposed study is quantitative), sampling bias must be avoided and sample size must be adequate. Resource allocation may involve funds, research personnel, time, and research participants. Researchers must decide if research is appropriate in the situation and where resources will come from. Feasibility and surge capacity must be assessed as adequate. Multi-centre research ethics review may be a way to use the REB resources available in the most effective and efficient manner. The consent process may be altered due to the circumstances of the emergency, but the autonomy of potential subjects must be respected. Populations which were previously vulnerable, such as the sick, may become more so, and other groups, e.g. health care workers during the SARS outbreak, may become newly vulnerable. Decision making capacity may need to be assessed prior to approaching a subject for consent to enroll him/her in a
research protocol. A single overseeing body, such as a university REB, may be the appropriate place for all emergency protocols to be cataloged so that there is a single source of information about all of the research that is taking place about the emergency. This might help to avoid overburdening subjects with too many protocols. While some investigators feel that participation in research should be obligatory\(^{128}\), there has been no discussion in the literature about how this would be affected by the context of a public emergency. The logical implication might be that the social obligation to participate would be even greater than usual during an epidemic, but this has not been discussed. The principles of justice and inclusiveness must be respected by a fair selection of research participants, but this must be balanced against the need for confidentiality of the information about victims of a public emergency. Justice must also be respected in the fairness of resource allocation.

At the end of the SARS outcomes study and after I had carried out the reflections contained in this chapter, I knew a lot about how researchers/clinicians working on the SARS outcomes study reacted to the outbreak, and I knew what the literature said about these issues. I did not know anything about what other kinds of research had taken place during the SARS outbreak and if there were other ethical and logistical issues that other SARS researchers had faced. REBs are a key piece of research ethical oversight and yet I realized that I knew very little about how REBs had reviewed the protocols submitted to them during the outbreak. In order to add to our knowledge about these issues, I designed an empirical study which asked about the issues that were faced by REBs during the SARS outbreak, how they were managed and about the ethical consequences of these issues and their solutions. This study uses a two pronged approach, the first which I call ‘Two REBs’ and the second which I call ‘Three Solitudes’ and is described in part III of this thesis.
Part III

‘TWO REBS’ & ‘THREE SOLITUDES’: AN INQUIRY INTO TWO REBS IN TORONTO DURING THE SARS OUTBREAK
CHAPTER 13: INTRODUCTION TO PART III

The objective of part III is to understand the impact of the SARS outbreak on research ethics review of SARS-related protocols. I undertook a study with two components. The first component which I call ‘Two REBs’ is a file review of the permanent records kept in two REBs in Toronto about the SARS-related protocols that each had reviewed as well as informal dialogue with the coordinators of each REB. The purpose of the file review was: 1) to acquire background information on the REBs previous year’s reviews, the nature of these proposals (industry-sponsored or investigator-driven) and the administrative format of the research ethics review (expedited or full board); 2) to glean information about the number of SARS proposals submitted, funding source for each protocol, time from submission to REB decision and other details that are kept in the files; and 3) to obtain the names of researchers who had submitted SARS-related proposals and of the REB members who had reviewed them. The names of researchers and REB reviewers were required to contact them to invite them to participate in the second component of this study.

The second component is a grounded theory inquiry that I call ‘Three Solitudes’. The objective was to develop a grounded theory about the impact of the SARS outbreak on the research ethics review system as it processed the SARS-related protocols that were submitted for REB review. The study includes the analysis of interviews with stakeholders about the process of REB submission and review that took place at the two institutions during the SARS outbreak. A second source of data for this component of the study was the REB files that are kept about each SARS protocol that was submitted. These were reviewed in order to provide clues about the
communication that took place during the review process. These data, along with the details from
the stakeholder interviews were analyzed and integrated into a theory that is presented in Chapter
17. Charmaz highlights Glaser’s suggestion that a grounded theorist should ask him/herself the
question “What is this a study of?”. The ‘Three Solitudes’ is a study of a system or an
organization under duress, where very basic questions about the structure of the system become
important. These questions include ‘what are the rules that need to be followed?’, ‘do public
health directives and infection control measures take precedence over the guidelines of the
TCPS?’ and ‘what is research in this context?’. As in the engineering model where a machine or
system is tested to find the weakest link, the natural experiment of research ethics review during
the SARS outbreak revealed several vulnerabilities in the system.

Organization of Part III

Chapter 13 Introduction to Part III

This current chapter provides an introduction to part III of the thesis and an outline of its
organization.

Chapter 14 Background (Two REBs/Three Solitudes) Literature review

Here I provide the objectives of the studies called ‘Two REBs’ and the ‘Three Solitudes’
and then discuss the organization of research ethics review in Canada at the time of the outbreak
and the distinction between research and public health practice. I focus on these areas because
they were raised in the analysis of both the studies that are presented in this part of the thesis.

Chapter 15 Methods (‘Two REBs’/‘Three Solitudes’
In this chapter, I provide detailed explanations of the methods that were used in each of the studies that are presented in the part III of the thesis. The ‘Two REBs’ study is a descriptive review of the permanent records kept by two research ethics boards’ (REBs) activity; the ‘Three Solitudes’ study is a grounded theory (GT) study, using the method as described by Charmaz. Details of the method and how I applied it are explored.

Chapter 16  Results and Discussion of ‘Two REBs’ Study

In this chapter, I focus on the results of the file review which explored the types of research projects conducted by SARS researchers. I document some details about the ethical review that was undertaken for each submitted protocol including type of review and time to approval if it was approved.

Chapter 17  Results and Discussion of the ‘Three Solitudes’ Study

The results of the analysis of the ‘Three Solitudes’ study are presented here in the form of a theory. It is a theory about the stressors that affected research ethics boards, the players involved in this process, how each of these players responded to the SARS outbreak and the interaction between them. Throughout the chapter, various parts of the theory are explained in detail and are supported by many quotes from my interviewees.

Chapter 18  Link to Part IV

In this short chapter, I present a rationale for the development of a framework for research ethics review that is informed by the ‘Two REBs’ and ‘Three Solitudes’ studies.
CHAPTER 14: ‘TWO REBS’ & ‘THREE SOLITUDES’: BACKGROUND

The objective of this part (part III) of the thesis is to clarify how research ethics review operated at the time of the SARS outbreak, and how SARS-related protocols were reviewed. In order to do this, I will first discuss the organization of research ethics review at the time of the outbreak, what rules applied, and who was involved in decision making and guideline development. I will also discuss some of the strengths and weaknesses of the research ethics review system in Canada. An outline of the problems facing the system under usual circumstances is provided. The REB system was already under attack prior to the SARS outbreak – not functioning very well according to some critics, mired in paperwork and inefficiencies. While much of the discussion originates from the United States, the problems are not fundamentally different in Canada as was elucidated by MacDonald.

First I discuss the Tri-Council Policy Statement (TCPS), the guidance document of the Canadian federal funding agencies, which specifically outlines the procedures that REBs should follow. As in the earlier chapters, I will refer to the older 1998 version of the TCPS as it was in force at the time of the SARS outbreak. I then present a very short section on other regulations, legislation, and guidance documents that are in some instances applicable to research involving humans that is carried out in Canada. Following this, I explore the governance of research ethics review in Canada. Fourth, I discuss institutional conflict of interest (COI) in the context of research ethics review. I then review the format of several multi-centre research ethics boards. Lastly I focus on the distinction between public health practice/surveillance/outbreak
management and research. I have chosen to focus on these areas because problems with each of them were raised in the analysis of the two studies discussed in this part of the thesis.

14.1 REB Structure in Canada as Mandated by the TCPS

As well as outlining the principles that need to be followed for research ethics review as described above in chapter 11, the TCPS outlines specific procedures to be used by REBs about composition of the board, scholarly review of protocols as part of the ethics review process, review procedures, in particular the use of a proportionate approach, meeting format and appeals. According to the TCPS, the membership of an REB must include at least five people, both men and women of which at least two have expertise in the areas of research covered by the REB, at least one who has knowledge of ethics, at least one who represents the community, and for biomedical research, at least one person who is knowledgeable in the relevant law. A quorum must be maintained for every protocol under discussion. In Canada, scholarly review of a protocol that poses more than minimal risk is required to ensure that the protocol can answer the question posed by the research. While this review need not be done in-house, the REB must satisfy itself that it has been performed elsewhere, perhaps by a funding agency or an independent external peer review panel. The review process begins with ‘an assessment, primarily from the viewpoint of the potential subjects, of the character, magnitude and probability of potential harms inherent in the research.’ 61 Once this initial assessment is carried out, the protocol is assigned to one of three levels of review: full REB, expedited by an individual or subgroup of the REB (minimal risk protocols, annual renewals or chart reviews), or departmental-level review for undergraduate projects. The concept of proportionality is to be applied at all levels of review. Face-to-face meetings are required, and described as “essential for adequate discussion” 61
2006, three years after the SARS outbreak, the Interagency Advisory Panel on Research Ethics (PRE), the federal body with stewardship responsibility for the evolution of the TCPS, was asked to discuss and interpret whether occasional videoconferences were consistent with the TCPS. Videoconferences are now permitted on an occasional basis. The TCPS also requires that a formal appeal process be in place. The institution is required to provide financial and administrative independence for the REB to carry out its mandate and they “must respect the authority delegated to it” ⁶¹, i.e., the REB should operate at arm’s length from the institution and be allowed to operate without interference. Most universities, large hospitals and other research institutions have set up their own research ethics board(s) since they are responsible for research carried out by its researchers, both inside the institution and at any other location. The TCPS does allow for an institution to delegate review of its research to another institution. However when this option is chosen, the home institution still retains responsibility and liability, and so must assure itself that adequate review is occurring. Delegation of research ethics review has been adopted by smaller hospitals that do not carry out enough research to warrant their own REB. Delegation also occurs in the case of multi-centre review of protocols that will be carried out by several centres. Multi-centre review is discussed in more detail below. While most REBs act independently of each other, REBs are free to form organizations to help provide educational resources and to promote dialogue between REB members and staff. Several educational initiatives have been supported by REBs and REB members across Canada. For example, Canadian Association of Research Ethics Boards (CAREB) is “a grassroots national membership organization intended to represent the interests of all Canadian Research Ethics Boards (REBs) and to reflect REB perspectives and concerns” ¹⁴¹.
14.2 Other Canadian Guidance Documents for Biomedical Research

There are two main sets of guidelines, one for federally funded research (the TCPS) and one that applies to drugs, biologics and medical devices. There are also a whole host of other guidance documents that apply to various other types of research, many of which overlap with the TCPS.

The TCPS is the research guideline that applies to the largest percentage of research involving human subjects conducted in Canada i.e., any research carried out in institutions that receive funding from one of the three councils as described in chapter 11. Since the TCPS has such wide applicability, it may also have ‘moral authority’ outside institutions that receive federal funding and are thus bound by a ‘memorandum of understanding’ (MOU) signed by the institution and one of the three research councils. Therefore, the descriptions that follow about other research guidance are very brief and only designed to provide a flavor for the other research guidelines applicable in Canada. While the funding source (along with institutional MOUs) is the main determinate of which guidance document applies, applicable supplementary guidelines can depend on the field of study and the location where the research will be conducted.  

Clinical trial regulations have been put in place by Health Canada and govern all clinical trials of drugs, biologics and devices regardless of location of the trial (hospital based or private office or in which province) and whether the product has been approved for sale in Canada or not. They have adopted as their standard the Guidelines of the International Conference on Harmonization of Good Clinical Practice (ICH-GCP)

“The "Guidelines for Good Clinical Practice" is an international ethical and scientific quality standard for designing, conducting, recording and reporting trials that involve the participation of human subjects, and is adopted by Health Canada which applies to drug and device studies undertaken by industry or with industry support”
When an investigator wants to study a drug, biologic or device, s/he must first apply to Health Canada with details of the proposed research, and then apply to the appropriate REB. When a pharmaceutical company wishes to use the results of the research for application for an American license of the product, the regulations of the FDA (US Food and Drug Administration) also apply.

As well as the federal guidelines described above, which apply across Canada, some provinces have legislation of their own. These regulations might apply when a researcher is based in that province as well as for research carried out there. For instance Quebec has the Civil Code and also les Fonds de la Recherche en Santé du Quebec (FRSQ) which plays an important role in regulating research conducted in Quebec that involves human subjects. The province of Newfoundland and Labrador has legislated a provincial REB; at the time of this writing it has yet to be proclaimed. The Alberta College of Physicians and Surgeons has established its own REB for physicians who are not part of an institution that has an REB, since it requires that all research conducted by physicians have research ethics review.

When a research project is funded by the American NIH (National Institutes of Health) or has some other US federal funding, the Common Rule must be followed, in which case OHRP (US Office for Human Research Protections) is the regulatory authority. Many large Canadian research institutions have obtained FWA (federalwide assurance) (similar to the MOUs between research institutions and the three Canadian research councils) and so follow the Common Rule for all research with humans as part of their FWA.

There are also several international codes which are influential. These include the Nuremberg Code, the Declaration of Helsinki, International Ethical Guidelines for Biomedical Research Involving Human Subjects prepared by the Council for International Organizations of Medical Sciences (CIOMS) in collaboration with the World Health Organization (WHO) and the
Council for International Organizations of Medical Sciences’s (CIOMS) International Ethical Guidelines for Epidemiological Studies. This last is particularly important for epidemiologic studies which may be conducted by public health units. In some cases, more than one set of guidelines apply and they do not always agree.

The Canadian guidelines have been described as: “an incomplete mosaic of rules that range from formal legal regulations, to administrative policies and voluntary guidelines”\textsuperscript{145}. The situation is confusing and complex and despite this myriad of guidelines, there are regulatory gaps – most notably research (except clinical trials of drugs and devices) conducted outside of hospitals, universities or government offices. While it is unclear how large this gap is, Downie says “it is reasonable to assume that it is a significant problem”\textsuperscript{144}.

My discussion here aims at giving a very general overview of the complexity of research ethics governance in Canada. For a more detailed discussion see Hadskis\textsuperscript{142} and for clinical trials regulations and the problems therein see Lemmens\textsuperscript{146,147}. The TCPS is emphasized throughout this thesis since it applies to all of the protocols reviewed at the two institutions that I studied, and was the only one required for the SARS study. In fact, all of the hospital-based research that I examined, except the treatment trials only required compliance with the TCPS. I would expect that most research proposed during a public health emergency and conducted by academic researchers (either hospital or university based) would be required to comply with only the TCPS, although some would need to comply with some of the supplementary guidelines mentioned above.

14.3 REB Governance and Its Challenges
In 2004, a group of American authors summarized the problems with the system of oversight of human research participants in the United States. They grouped fifteen problems into three categories: structural problems that relate to their federal regulations, procedural problems about the way individual IRBs operate, and performance assessment problems. Of particular relevance in the context of a public emergency are three from the first group: no effective mechanism for IRBs to address major ethical issues, inherent institutional conflict of interest (discussed in more detail below) and repetitive IRB review; and two from the second group: time-consuming review process and excessive focus on consent forms. Because there is no formal mechanism for REBs not only to address major ethical issues but also to form policies to deal with unusual circumstances, REBs may flounder when asked to review unusual protocols dealing with a situation where the risks and potential harms to the community and to research participants may not be well defined as in the case of a public emergency. The current system where a multi-centre trial is reviewed by every site that participates in the trial is wasteful and redundant. Although there is no evidence that these multiple reviews help to protect the research participants, there are legitimate local issues (such as feasibility at the local site and review of qualifications of local research staff) that deserve review. Multi-centre review is discussed in more detail below. To adequately review a complex protocol is time-consuming and since REBs are chronically understaffed and often rely on volunteers, they often fall behind in the performance of these reviews. This problem is exacerbated by the lack of adequate funding. Lastly, there is thought to be an excessive focus by REBs on informed consent forms. Consent forms are discussed in more detail in section 11.52. While the Canadian system does not have a legislated system (although the entire drug, biologics and devices review system is legislated, the research ethics review of these products is organized through guidance documents), but rather a
guiding research ethics review document (the Tri-Council Policy Statement), most of the problems are similar to those encountered in the American system. Both systems have two sets of guidelines/regulations, one for drugs, biologics and medical devices and one for federally funded institutions, but the US has clear regulations, a better oversight structure (although with some room for improvement) and penalties.

In 2005, a special edition of Health Law Review focused on Canadian governance for ethical research involving humans and five major problems with the Canadian system were cited: 1) the complexity and fragmentation of the Canadian governance arrangement, 2) the structure of the system that focuses attention on the paperwork and not enough on the protection of subjects, 3) lack of monitoring and auditing processes for on-going and completed research, 4) research subjects being treated as passive rather than active participants in the governance process, and 5) systematic conflict of interest due to lack of arm’s length oversight. All of these issues have also been discussed at length about the US system. These are themes that were certainly present during the SARS outbreak, and several of these were raised in the stakeholders’ interviews, the results of which are described in Chapter 17.

14.4 Conflict of Interest

The 1998 version of the TCPS devotes a whole chapter (chapter 4) albeit a short one, to the issue of conflict of interest. Article C says:

“The REB must act independently from the parent organization. Therefore, institutions must respect the autonomy of the REB and ensure that the REB has the appropriate financial and administrative independence to fulfil its primary duties. Situations may arise where the parent organization has a strong interest in seeing a project approved before all ethical questions are resolved. As the body mandated to maintain high ethical standards, however, the public trust and integrity of the research process require that the REB maintain an arm’s-length relationship with
the parent organization and avoid and manage real or apparent conflicts of interest.” 

This issue was considered to be important enough that the chapter in the revised draft 2nd edition TCPS is much expanded. It advises institutions and REBs to be transparent in all their interactions, and to develop standard operating procedures that should be followed. It also suggests several mechanisms to minimize conflicts of interest such as central institutional conflicts of interest committees and refining roles and “responsibilities and reporting lines to avoid, minimize or manage the potential for conflicts”.

The problem of institutional COI has been discussed by many authors. While most of these authors focus on financial conflict, the same problems exist with regards to other conflicts of interest. Pressure to approve protocols from management of the institution for whatever reason is not acceptable. Downie states

“independent review is largely illusory in our current system. Conflicts of interest are pervasive in the administration of ethics review systems, particularly those that are situated in institutions, and these conflicts have the potential to reduce independence.”

Emanuel et al. as part of the review mentioned above also discuss inherent institutional conflicts of interest in the research ethics review system. They highlight the facts that IRBs receive their operating funds from the institution for which they review research proposals and that many of the IRB members are colleagues of the researchers who would like their protocols approved. Several types of reforms have been proposed to deal with these problems in the United States (accreditation, IRB education, central IRB and several pieces of legislation), but Emanuel et al. suggest that each of these solutions would only partially solve any of the structural issues that are problematic.
14.5 Multi-Centre Review

The TCPS allows for multi-centre review, but says that “principles of institutional accountability require that each local REB be responsible for the ethical acceptability of research undertaken within its institution.” This may be accomplished by designating another REB to be the REB of record, after it is assured that this other REB is fully competent to review the protocol in question. The home REB keeps track of the protocols implemented at its own site and retains responsibility and liability for any implications of the designated REBs decisions. Details about which REB would be responsible for follow-up monitoring would be dealt with on an individual basis.

Several models of centralized review are reported and adoption of this type of model can potentially help to decrease the redundancy of submissions to multiple REBs. Centralized review boards can be classified into three types: 1) those that review only protocols about a specific disease types such as cancer or AIDS, which I will call central REBs, 2) cooperative REBs, that is, those affiliated with and operated by one of several centers that use it, and, 3) noninstitutional REBs, those that are for hire and may or may not sell other services such as clinical research organizations that have the capacity to coordinate trials as well as ethically evaluate them, e.g., Ethica Clinical Research Inc.

A central institutional review board (IRB) based on disease studied was implemented by the National Cancer Institute in the United States and was described early in its existence. It is a central IRB that reviews multi-centre trials conducted about different cancers. The authors who discussed this system were unsure whether this would ultimately improve efficiency or just represent another layer of bureaucracy. This IRB remains active and lists on its web site over 200 protocols that it has reviewed. Since 2004, it has reviewed pediatric cancer trials as well
as trials enrolling adults. More recently, Chaddah has written of the Ontario Cancer Research Ethics Board (OCREB) as a central REB that works. \textsuperscript{155} It is a non-institutional, but multi-affiliated REB that is not run for profit. Saginur et al. also report on this REB and describe the four motivations for its formation: 1) need for review of protocols by multiple experts in the field, 2) need for timely review, 3) need to streamline serious adverse event (SAE) reporting, and 4) the need for more coordinated and perhaps more influential dealings with drug companies. \textsuperscript{154} All of these would likely be relevant in a public emergency, with the fourth one being particularly relevant for treatment trials during an outbreak of infectious disease.

Another model that has had some success is a cooperative IRB. Koski et al. provides some details on how two of these (Multicenter Academic Clinical Research Organization (MACRO) and Biomedical Research Alliance of New York (BRANY)) work and discusses the pros and cons of each IRB.\textsuperscript{156} Several Canadian cooperatives have also been described and some authors comment on the importance of building trust among the sponsoring institutions of these cooperatives and the REBs.\textsuperscript{157}

Noninstitutional REBs are similar in some respects to central REBs although they are not affiliated with a particular institution.\textsuperscript{158} These are for-profit businesses that sometimes have as their sole task to review the ethical aspects of research projects. There is an inherent risk of conflict of interest in this type of REB.\textsuperscript{158} These corporations are paid to evaluate and approve research projects. While I have not seen data to this effect, it may be logical to assume that if these are perceived to reject too many protocols, researchers will no longer use their services. This may invite ‘REB shopping’ where investigators submit their protocols to the noninstitutional REB that is seen as the ‘easiest’. Should this model become more prevalent, some regulation may be required to prevent and to police this; something as simple as requiring a researcher to list all
other REBs that have reviewed a protocol and their list of concerns might go a long way to help this situation.

There are advantages and disadvantages to each of these systems although each has the potential to reduce the redundant paperwork of many REB submissions of the same protocol. All are slightly more at arm’s length than a board that is operated by the institution whose protocols it reviews. Usually a central review board is quicker than an institutional board especially those that are run for profit.\textsuperscript{156} A recent Association of American Medical Colleges survey documents some of the disadvantages of central IRBs (defined as any non-institutional board or cooperative arrangement).\textsuperscript{160} These included concerns about potential liability, additional cost, absence of local representation, and inability to assess the quality of services rendered. An advantage of an REB specializing in a particular disease is that there are many experts from the specific field on hand. In theory an AIDS board could be ready at a moment’s notice to review any infectious disease (ID) protocol as these boards have many ID specialists. This feature could be very useful in an outbreak of any infectious disease. The issue of liability may be particularly challenging as contracts between the institution to carry out the research and the central REB may be negotiated on a per protocol basis. If this process just shifts the work load from the REB to the contract department the institution is financially no further ahead. This may not be an issue for cooperative boards with fewer boards involved as perhaps many contracts could include many standard clauses. Thus, there are complicated hurdles to be overcome before this type of model is adopted more universally. All of these models took time to develop and the processes continue to evolve.\textsuperscript{153-158}

After the bombing in Oklahoma City, a single IRB oversaw all disaster-related research protocols.\textsuperscript{64} This occurred as a result of the governor of Oklahoma’s request that all disaster-
related research be approved by the University of Oklahoma’s IRB and the state Commissioner of Health’s requirement that all disaster-related injuries be reported to the state Department of Health. (Similarly, SARS was declared to be a reportable illness by public health officials in Canada). These two acts by the appropriate politician/political appointee meant that there were central registries for both all the injuries that occurred and all the research that ensued. It also meant that when two researchers submitted similar projects, they were encouraged to work together to save costs, personnel and most importantly to only approach research subjects once. This board then functioned as an *ad hoc* central IRB with a group of IRB members who were used to working together.

### 14.6 Distinction between Public Health Practice and Research

One important and problematic area for REBs during the Toronto SARS outbreak was the distinction between practice and research. There are many different distinctions between these two areas, but I will focus primarily on public health practice (particularly outbreak management) versus epidemiological research. There is a wide grey zone between the two and REBs, researchers, and public health personnel continue to debate which types of projects fall within the scope of research ethics review. This controversy is not new. In 1979, Robert Levine discussed some of the thinking that occurred about this issue as the Belmont Report was being written.

Several strategies have been suggested and different organizations use different aspects of the project to differentiate research from public health practice. Three schools of thought have emerged in this debate. First is the suggestion that it is the intent of the practitioner that determines if the work is research or practice. The second group claims that it is the institution
to which the practitioner reports that is important and the third group proposed that public health practitioners and researchers should evaluate all of their work for adherence to ethical principles. Snider and Stroup, articulating the Centers for Disease Control and Prevention’s (CDC) official position, suggest that the intent of the investigator is what is the key issue. They state that:

“The major distinction between research and practice is in the intent for which the activity is designed. The intent of research is to contribute to or generate generalizable knowledge; the intent of public health practice is to conduct programs to prevent disease and injury and improve the health of communities.”

They point out that timely outbreak investigation and surveillance cannot be effectively carried out if there is a need to submit a proposal for institutional review board (IRB) approval. The US federal policy about the protection of participants in research involving human subjects (the Common Rule) requires that research projects, but not routine public health activities, be approved by these bodies. Thus the definition of what is research and what is not, is pivotal. The CDC in 1993 defined three areas that they consider to be practice: 1) public health surveillance 2) emergency responses and 3) program evaluation. Surveillance is mandated by law and while generalizable knowledge may result from it, the primary purpose is to monitor disease prevalence and incidence and to take action when necessary. In reply to this viewpoint, Mariner takes issue with the use of intent as the deciding factor. She comments: “the problem with using intent is that it does not address the difficulty many researchers have in being honest about their intentions”. She feels that public health researchers may ‘disguise’ their research as practice. She concludes by stating: “rather than seek new ways to avoid adherence to ethical standards, the public health community would do well to voluntarily adopt higher ethical standards for all its activities.” Perhaps as suggested by MacQueen et al., we should strive to
ensure that all public health projects are evaluated by some ethical body and worry less about whether the project is deemed to be research or not. However, such a board might be too costly and too burdensome administratively to be a viable option for public health agencies.

Other authors suggest that it is the person or agency who is conducting the project that matters. Projects that are carried out by public health officials are surveillance or outbreak management, and thus not subject to REB approval. The same project under the direction of an academic researcher is research and as such must be submitted to the REB for review. In Toronto, until recently, most public health units did not have an REB and the few research projects that were carried out were reviewed by the REB of the university to which the public health official was affiliated.

The intent argument is also discussed by Fairchild. She cites an example where the Alaskan state public health department did not want to “delegate the decision making process to an IRB” so they returned the allocated funds to the federal government and as a result a worthwhile project (surveillance for fetal alcohol syndrome) did not take place. Because the notion of intent is subject to vastly different interpretations, she calls for an articulation of ethical principles for public health practitioners. While this would not solve the problem of research versus surveillance, such an articulation of ethical principles would “render what has been an ongoing and tortured effort to distinguish such activities from research less momentous.” She carries this argument further in her writings with Bayer by concluding:

“It is inappropriate to regard ethical oversight strictly as an impediment. In the context of public health surveillance, it can serve as a means of avoiding inadvertent breaches in confidentiality and stigma; it can help to ensure that the public understands that surveillance will occur and what purposes it serves; it can protect politically sensitive surveillance efforts. There is, after all, an ethical mandate to undertake surveillance that enhances the well-being of populations.”
Internationally, the Council for International Organizations of Medical Sciences (CIOMS) in collaboration with the World Health Organization (WHO) has recently (2008) published the International Ethical Guidelines for Epidemiological Studies. This is a revision of the earlier (2002) International Ethical Guidelines for Biomedical Research Involving Human Subjects and it states that:

“In the case of interventional studies, the present Guidelines [for epidemiological studies] are generally the same as those in the 2002 document, but whenever appropriate the commentary has been focused on issues that arise in epidemiological rather than biomedical research. . . . The present Guidelines address observational studies by noting, in the commentary, the ways in which it may be appropriate to treat such research differently than interventional studies (for example, regarding informed consent)”

The 2008 document addresses the issue of practice versus research in one small section in the introduction. It speaks briefly about the definition of research in this context, particularly the ‘generalizable knowledge’ definition. (Where research is defined as a systematic activity that is designed to contribute to generalizable knowledge). However, the document also states:

“But the [generalizable knowledge] definition works less well in separating practice from research in the field of epidemiology. Many studies using the tools of epidemiology which are performed on a regular basis by public health agencies, such as routine surveillance for disease outbreaks, are correctly viewed as “practice” even though the information produced may contribute to generalizable knowledge. Thus, in carrying out their activities epidemiologists (and others examining the activities) need to apply careful judgment to determine whether the activity should be classified as research or practice.”

Thus it remains difficult to clearly differentiate research and practice according to this guidance document.

A distinction must be made between research that is carried out about the issues that are specific to a public emergency and routine research that continues during the emergency. For the former, the revised draft 2nd edition of the TCPS allows REBs to follow modified procedures and practices to be requested by the investigators and at the discretion of the REB. However, for the
later type of research, ethics approval and monitoring should continue according to normal 
principles and procedures. It might be the case, that this research be suspended, and only resumes 
one the publicly declared emergency is over if REBs are not able to function as usual.

14.7 Conclusion

In this chapter I discuss REB structure in Canada as mandated by the TCPS and mention 
many other Canadian guidance documents for biomedical research. It is important to understand 
these guidelines in order to evaluate the ability of REBs to comply with them during the SARS 
outbreak. I review REB governance and its challenges in order to elucidate the problems with the 
system before and during the outbreak. In theory, a system already in crisis will perform even less 
well when subjected to the additional stressors of an outbreak. Sections on conflict of interest 
(COI) and multi-centre review are included because both of these areas were problematic during 
the outbreak. COI is important because there was a lot at stake for institutions and governments, 
researchers and REBs, as well as the public at large. The need to protect research subjects was 
high and time was short and multi-centre review might have helped to meet these objectives. The 
distinction between public health practice and research is an ongoing problem and it was 
problematic during the SARS outbreak.
CHAPTER 15: ‘TWO REBS’ & ‘THREE SOLITUDES’: METHODS

The purpose of this chapter is to describe in detail the methods used in the ‘Two REBs’ and ‘Three Solitudes’ studies of research ethics review at two institutions during the SARS outbreak. The objective of the combined studies is to understand the impact of the SARS outbreak on research ethics review of SARS-related protocols. While many ongoing research projects and the review of new submissions about other diseases must also have been altered because of the circumstances of the public emergency, it is beyond the scope of this thesis to discuss those and I will limit my discussion to those proposals relevant to the SARS outbreak and its impact.

There are two components to this study: a descriptive review of the permanent records kept by two research ethics boards’ (REBs) activity during the outbreak in Toronto called ‘Two REBs’ and a grounded theory study called ‘Three Solitudes’. The grounded theory study uses two data sources: 1) transcripts of semi-structured interviews with REB members who reviewed SARS protocols, SARS researchers and public health officials; and 2) the permanent REB files that are kept as a record of SARS-related submissions and the review that ensued.

This chapter begins with a description of the methods used in the file review that I performed on each of two Research Ethics Boards (REBs) from which I recruited interviewees. One of these is a large academic quaternary care centre and the other is a large urban community hospital that was one of the two epicentres of the SARS outbreak in Toronto. Following this is a description of the grounded theory methods that I used to collect data and analyze them. This includes both the interviews with key informants who were familiar with the review process at one
of my two target institutions as well as the information I gleaned from the review of the permanent REB files.

15.1 The File Review

15.11 Research Design

The objective of the file review was to determine the type and number of research projects submitted for research ethics review during the SARS outbreak and to document the time from submission to completion of the review. As well, the nature of research participants in these studies and their funding sources were noted. I submitted my research proposal to two REBs and was given permission by each to examine their permanent records of all SARS-related submissions and to interact with their research ethics coordinators. They provided information on the number of protocols, expedited reviews and industry-driven projects in the year prior to the outbreak, which I used as contextual information about each of the REBs. The file review was conducted in 2006-7, three years after the end of the outbreak, and therefore was not restricted by the infection control measures that had been in place during the outbreak.

15.12 Participants

15.121 Sampling Frame

The sampling frame for the research ethics board file review was every REB in the greater Toronto area that had reviewed SARS-related protocols. These institutions fall into two categories – academic centres and community hospitals. Some hospitals saw just a few SARS patients while others saw many (range of 1-87 patients/site). Public health units in the Toronto area in 2003 did not have REBs to review proposed research projects; SARS-related projects with a public health
practitioner as the principal investigator were reviewed by the university with which s/he was affiliated.

Before selecting the sites that I would study, I made several assumptions about where SARS-related research took place. Specifically, I assumed that 1) more research was conducted in academic centres compared to community hospitals, since this is where researchers hold appointments; 2) that researchers submitted their protocols to their academic centres’ REBs as well as to the other locations where they sought participants; 3) that within non-academic institutions, more research protocols were carried out at hospitals where there were more patients; and 4) that more research was carried out at the two epicentres of spread compared to other community hospitals. I did not confirm these assumptions by calling the eighteen hospitals and the three universities in Toronto. It might seem that this would have been an easy task, but based on my interactions with the two REBs where I conducted my file review, I believe that REBs would not have divulged this information without a formal REB application at each site. In discussion with my committee, we decided that the amount of information that might be obtained from the exercise of calling REBs would not have been worth the amount of work this would have entailed.

15.122 Sample

I chose two institutions to study. Using the assumptions stated above, I selected one academic centre and one community hospital. I chose one of each as I postulated that the experiences with their REBs might be different from each other and I wanted to maximize the range of experiences in my interviewees. I also wanted to maximize the number of different protocols that I would examine and so the community hospital selected was one of the two
epicentres of disease. I chose this one rather than the other one because I knew someone who had worked there during the outbreak and was told that the REB had not been operating as it normally did. It is a large hospital whose focus is community medicine. Sixty-eight SARS patients were cared for there. The academic centre that I chose is a large quaternary care, academic research centre; it has multiple REBs and had cared for 18 SARS patients. This center was chosen rather than another academic centre because I had a working relationship with this REB, although I was not a member of the REB at the time of the SARS outbreak. Each of the selected hospitals had seen enough SARS patients for me to postulate that many protocols had been submitted to their REB. I wanted to examine submissions that were made at the time of greatest uncertainty and least information about the causative organism, the illness and the impact on the health care system, because I thought that this would be the time when changes to the REB process might be the most extreme and when the time pressure was most urgent. Because of this, I limited my file review to submissions made in 2003 to capture any changes necessitated by the need for speed or adherence to infection control measures. Both of the institutions selected have received funding from one of the three federal research funding bodies (CIHR, NSERC, and/or SSHRC) and strive to be in compliance with the TCPS.

15.13 Data Collection

At the community hospital REB, the SARS protocols are filed using a separate numbering system, so the research ethics coordinator was quickly able to find the permanent records of these submissions. At the academic centre REB, a computerized database of all REB submissions is maintained. The research ethics coordinator searched for the word ‘SARS’ in the title of all protocols submitted between January and December of 2003. I also reviewed one other pertinent
protocol. The paper files were then pulled. The file for one of these protocols was never found and there was minimal detail available on that protocol in the computerized record; perhaps this submission was not completed.

Using the data collection form (Appendix III) I had developed and that had been approved by both REBs, I sat with my laptop in the REB offices and extracted the required data. I was particularly interested in what types of research projects were submitted, how many studies were submitted to both institutions, the time from submission to completion of the review, funding sources and types of participants researchers were interested in studying. These data were entered into the relational database software Paradox (2003 Corel Corporation. WordPerfect Office 11.0).

15.14 Analysis

The results of the REB file review are descriptive. Microsoft® Excel 2003 (Part of Microsoft Office Professional Edition 2003) was used to tabulate counts, means and medians. A table was constructed to describe the protocols submitted, to show which center they were submitted to and to highlight the time from submission to approval. In order to classify studies, I sorted them into categories according to who was eligible to participate: 1) HCW: those involving health care workers, 2) patients: those involving SARS patients, their radiographs, tissues or blood samples, 3) non-SARS patients and 4) healthy volunteers. Since many investigators were interested in studying the psychological or social impact of the outbreak, I also highlighted the impact studies. In order to visualize which participants were eligible for the impact studies, a Venn diagram was constructed.

15.15 Confidentiality
All data recorded from this file review are kept on a password protected laptop computer. It was kept in a secure place at all times and the investigator was aware of the sensitive nature of the data. Encryption was not mandatory at that time.

15.2 Grounded Theory Study

15.21 Research Design

The objective of the ‘Three Solitudes’ study is to build a theory about the impact of the SARS outbreak on the research ethics review system as it processed SARS-related protocols submitted for REB review. Grounded theory is used to analyze my two data sources: 1) semi-structured interviews and 2) the permanent records of SARS-related submissions.

I felt that qualitative interviews were the best way to explore the research experiences of the SARS investigators and the REB members who had reviewed their protocols. “Good qualitative data are more likely to lead to serendipitous findings and to new integrations; they help researchers to get beyond initial conceptions and to generate or revise conceptual frameworks.”

Once I had decided on this method of data collection, I needed to select which tradition of qualitative research I would follow. After reading several general texts about various methods, I had narrowed it down to two that seemed to me to be the most suitable to my question: grounded theory and case study. Several things attracted me to grounded theory. Charmaz says that grounded theory is a “method to study process’ and I wanted to investigate how the research review process had been affected by the unusual circumstances of an outbreak of an infectious disease caused by a novel pathogen. I liked the fact that one doesn’t need to start with a literature review that might direct the inquiry. I wanted to allow REB members to tell me what important issues had arisen during their review of SARS-related protocols and to stay as close to
what my participants were saying as possible in the formation of my theory. I liked the constant
comparative method that is central to grounded theory as is described below; I felt that this would
ensure that I stayed close to what my participants were saying. I also liked the fact that there are
well defined methods of rigor also described below. There was also expertise with this method
among my committee members which I knew would help me learn what to me was a new
approach.

Having read through the files about the SARS-related submissions, I knew that there was
more information in them than I had extracted for the file review portion of the study. Grounded
theory allows for data from multiple sources, and any type of data can be incorporated into the
analysis. I therefore re-read the records of the submissions, without a structured data collection
form to better understand the communication strategies that were used between REBs and
researchers.

15.22 Data Source #1 - Interview Participants

15.221 Sampling Frame

All REB members at the two selected institutions who had reviewed SARS protocols
(both REB members and REB coordinators if they were involved in reviews) and all principal and
co-investigators listed on the protocols were eligible to participate in the qualitative interview
section of my study. I felt that these two institutions would provide enough REB members and
investigators for my study and that these people would cover a large range of experiences. I
postulated that different REBs might emphasize different ethical issues that were felt to be
important to their communities and that different ethical issues would arise in different types of
methodologies involving different groups of participants.
15.222 Recruitment/Sampling Strategies

There were 89 investigators listed as either principal investigator (PI) or co-investigators (Co-I) on the SARS-submissions reviewed at the two centres. There was one group of about 5-7 people who were involved on several protocols, who thus had a range of exposure to many challenges involving outbreak research and also many researchers who conducted only one protocol. Many of the investigators listed on the protocols at the community hospital were academics who practiced at one of the downtown university hospitals. There were just nine co-investigators based at the community hospital.

In order to contact potential interviewees and be respectful of their privacy, an e-mail was sent from the REB office to SARS researchers asking recipients to contact me if they would agree to be interviewed about their SARS research experience (see Appendix II for the letter). In addition to the e-mail, a letter was sent to potential interviewees at the community hospital. Several of them were no longer employees of the hospital and the letters were sent to their homes when these addresses could be obtained from the human resources department of the hospital. I received no replies from researchers at the community hospital. In order to improve my sample from this group, I requested that the REB allow me to phone people with whom I wanted to speak. They refused this, saying that people should not have to do something in order not to be a part of a study. Thus I was restricted somewhat by the passive recruitment strategy that was required to meet the REB stipulations. In order to submit my request to the REB at the community hospital, I was required to list a Co-I from within the institution since I was not on staff there myself. This was the only investigator from the community hospital who agreed to be interviewed and she re-iterated to me several times that although she did collect some research samples, her primary role during the SARS outbreak was treating patients and not designing or
analyzing research protocols. I was surprised by this low rate of participation and wondered if there were other ongoing issues within the hospital that made individuals reluctant to voice their thoughts about this trying time at their institution e.g. litigation. During the period that I was involved in data collection, several lawsuits were before the court. Several nurses’ groups sought to show that the Ontario government had reacted negligently to the epidemic, and thus the subject may have been too sensitive to discuss with an outside researcher.

To manage the number of potential interviewees at the academic centre (82 identified), I had the REB office send e-mails to the first eighteen names on my alphabetically sorted list. By chance, many senior researchers who were heavily involved with SARS research were among this group and several of them contacted me about being interviewed. Several researchers were known to me from my work with the outcomes study and some of these people were interviewed. From this group of researchers, I was able to interview four individuals who conducted their research exclusively at the academic centre and another five who worked at both of the hospitals that I was interested in. With the data provided by these people, and as difficult as saturation is to be sure of, I felt that I had reached saturation in the categories that were relevant to researchers and that a further request for participants was not required. The notion of saturation and adequacy of sample size is dealt with more thoroughly and explicitly and in the sample size section below.

Assessing who were the appropriate REB members for me to interview for my study proved to be slightly more challenging than finding researchers to interview. At the community hospital, the computer generated list of reviewers that I was given revealed twenty-one individuals who had reviewed at least one protocol. All were e-mailed and sent hard copy letters about being interviewed for my study. From this invitation, I only received one reply and when I spoke with her, she said that she had only volunteered on the REB after the SARS outbreak was over. One of
the REB members from the community hospital knew me and my interest in this area and volunteered to be interviewed even before the e-mail was sent out. By chance, she had also conducted a research study at the community hospital and thus was able to discuss her role as both REB member and SARS researcher. (Her primary role, however, was with the REB) This person called several colleagues who had served on the REB and asked if they would agree to be interviewed. Only one person volunteered. As a result of the discussion mentioned above about whether I could place a phone call to individuals I wished to interview, one of the discussants realized that she was on the list and volunteered to be interviewed. One of the REB members that I interviewed said that there were really just five people who had significant involvement reviewing SARS-related protocols at the community hospital and that two of them were particularly important in the deliberations about the ethical issues involved. I was able to interview both of these individuals. Thus along with the person that I knew and the individual that she recruited for me, I had three interviews with REB members from the community hospital. Again, I was surprised by the difficulty that I had in obtaining interviewees. I wondered if perhaps the SARS outbreak had been so stressful for the people at this hospital that they were unable to revisit their experiences.

At the academic research centre, it became clear early in my discussion with the chair and the ethics coordinator that there were just two people who had reviewed SARS-related protocols with minimal outside consultation. Both of the REB members at the academic centre were known to me, and so I contacted these two people personally, and both agreed to the interview. Thus I felt that I obtained information from all of the key people involved with reviewing SARS-related protocols for ethical problems at the two institutions in which I was interested.
I had a much better response rate from the academics than from those at the community hospital. This may have been because many of the academics knew me, whereas I did not know my participants from the community hospital. One of the people from the community hospital that I interviewed speculated that perhaps the SARS outbreak was so traumatic at that centre that people were unwilling to think or talk about the experience and so were not willing to be interviewed. I do not know if this skewed the data that I acquired and if there were other important issues that were not discussed with me e.g., the ongoing law suits mentioned above. It is possible that this resulted in lack of depth in some of my categories that were particularly pertinent to this setting.

Theoretical sampling occurs when a researcher seeks out data to enrich the developing theory. Charmaz says that the purpose of theoretical sampling “is to obtain data to help you explicate your categories” and that “it pertains only to conceptual and theoretical development”. As the interviews progressed, public health officials were mentioned by several researchers as having valuable knowledge and experience that might be helpful to me, and I thus contacted and interviewed two members of the Toronto Public Health team who had responded to the SARS outbreak. This sequential referral strategy was also used when several of my interviewees suggested others who could inform me more fully about some of my questions. Sequential referral is one of processes through which theoretical sampling occurs as I chose to contact only those individuals whom I felt could deepen the categories on which I was working and advance my theory. I used theoretical sampling to further my understanding of the interaction between public health and REBs, to elucidate the interactions between public health and researchers and public health and REBs particularly in the community hospital setting. In order to fill in the theoretical gaps about how public health personnel view the distinction between research and
practice, I sought representatives of the public health unit that dealt with containment of the outbreak. I anticipated that my data would be richer with the addition of this new perspective. Using theoretical sampling, someone who played a role in the academic centre’s outbreak command centre was suggested to me by one of my participants and this individual was also interviewed.

15.223 Sample Size

I anticipated that about 20 to 25 participants would provide a sufficiently large pool of data. This estimate was based on my early reading about qualitative methods (which suggested that sample sizes of 10-30 can provide enough detail depending on the topic) and on the previous experience of my committee members. I had four potential groups of individuals, i.e., REB members from both sites and investigators from both sites. When I initially wrote my proposal, I thought that six interviews in each group would be possible and would yield a sufficiently rich data set of 24 interviews from which to build my theory. In practice and as discussed in detail above, it was not as straightforward as this. There was overlap between researchers submitting protocols to the two centres and contacting REB members was more complex than I anticipated.

In order to assess if enough data have been collected, grounded theorists agree that the categories that have been developed should be saturated. At first glance, this seems to be an easy concept. However, when one delves deeper, it becomes clear that the concept of saturation and how it should be operationalized is not well defined in the literature. Strauss & Corbin state that saturation is reached when “(a) no new or relevant data seem to emerge regarding a category (b) the category is well developed in terms of its properties and dimensions demonstrating variation
and (c) the relationships among categories are well established and validated”. They also say that the analysis must account for most of the possible variation in the categories. Charmaz agrees, saying that categories are saturated “when gathering fresh data no longer sparks new theoretical insights, nor reveals new properties of these core theoretical categories”. However, she then goes on to say that when common or trivial categories are chosen, saturation may be achieved easily. When more complex categories are identified, more data need to be collected. Morse comments that saturation has been reached when the investigator proclaims it so! Dey (quoted in Charmaz) suggests that a better term to reflect what researchers actually do would be ‘theoretical sufficiency’. After the analysis of the nineteen interviews and the memos from the REB file review, I felt that my categories were rich, and that I understood the interactions between them and that no new insights would be gathered by pursuing the analysis further or collecting more data. However, I will never know if the other people that I was not able to interview might have a different perspective that could have further enriched my categories. There might have been something systematically different about their experiences that I could not capture from the individuals with whom I spoke.

15.23 Data Source #2 - Permanent REB Records of SARS-related Submissions

The second data source used for the grounded theory portion of the ‘Three Solitudes’ study was a re-review of all the permanent REB records of SARS-related submissions. This time I was looking for process items, as opposed to the details of the protocols that I had noted earlier. I was particularly interested in correspondence, e-mail trails and notes about telephone conversations.
15.24 Data Collection - Interviews

Interview data were collected through semi-structured interviews using open-ended questions based on an interview guide (See Appendix III). Each interview began with the subject reading and signing the consent form, a copy of which was always left with her. Two recording devices were used for each interview, a digital device and an audio recorder for back-up.

Interviews were generally carried out in the interviewee’s office or a conference room nearby, although one was conducted in the participant’s home, one over the phone and another in a coffee shop of the community hospital. The first question was always: “What was your research role during SARS?” and the second: “How did the SARS outbreak affect your practice of research or research ethics review?”. In response to these questions, most people talked with very little probing or further direction from me. “An interview is a directed conversation; an extensive interview permits an in-depth exploration of a particular topic with a person who has had the relevant experience”. Occasionally, I stopped a participant to ask her to clarify something that I did not understand. Once an interviewee felt that she had answered my questions, I directed her back to a point about which I wanted more detail or asked about points that had been raised in previous interviews. Thus, I was able to elicit rich data from my participants by probing and encouraging them to fully explain to me what their research and review experiences were like.

Two examples of probing follow with the probes in **bold**:

*from interview #6*

R *And so, if we have that infrastructure functioning... you know if we believed in doing this kind of work. If we had and, and part of the reason people don’t do it, you know... eh... I run ... TB surveillance ...that’s 34 ethics approvals every year. Every piece of surveillance we do. There are just not very many people who are willing to deal with that kind of shit, fundamentally, you know...*

I *yeah... right... **And why is that research and not surveillance?***

R *Well, well, no... If public health were doing it for public health it would be surveillance. If I’m doing it for research purposes, it’s research.*
Okay...
Unequivocally, okay...
I'm still trying to grapple with the distinction... that...

from interview #4
And um, tsk, there is su.. some centres were very happy to co.. uh to cooperate, others were, were less happy, eh, they all, uh... did ultimately. But...
But when you say centres was it the investigators or .. um.. clinicians.. or the REBs or who, who did you have to negotiate that with?
Um.. no problems with the REBs except for sometimes in, in uh, in timing.. of, you know like we s.. you we still wanted to try to do things fairly quickly.

At the end of each interview, I always asked if there was anything else that the participant wanted to add. I then thanked her and turned off the recorders. Sometimes, participants continued the discussion in a more informal manner after the recorders were off. I used a memo to note any important points raised in these non-recorded discussions. Charmaz speaks of memos as “the pivotal intermediate step between data collection and writing drafts of papers”. They are a recording of thoughts and ideas jotted down as soon as they come to mind and may be in a formal writing style or just a few phrases. These formal or informal thoughts become data and are analyzed along with other data already collected.

I downloaded the audio file of the interviews from the digital recorder to my computer and sent it electronically to the transcriber via the secure web site that she maintains specifically for the purpose of transmitting electronic files back and forth. When the transcriptions were complete, the web site was again used to retrieve the Word documents that the transcriber had prepared. I then listened to the recordings, corrected any transcription errors and inserted anything that the transcriber had missed. I also deleted the names of people who were mentioned by the participants and left only their initials. This copy of the interview was then kept as the original.
In order to better comprehend the sense of the statements and to make the transcripts more readable, the umhs, ahs and repetitive wordings often used by all of us as we speak were ‘cleaned up’. Some analysts feel that it is important to analyze the pauses, umhs and ahs, in order to characterize hesitancies, passion and/or uncertainties about the subject matter or about the speakers underlying feelings about the topic. Many unspoken messages that we portray are contained in these phrases and I realize that I precluded their analysis in taking these data out of the transcripts that I used. While I acknowledge that they are important in many contexts, I did not feel that these linguistic characteristics were relevant to the type of information that I was eliciting. If I decide at some point in the future that this might add to my theory, the original transcripts are still available. However, for the purposes of this analysis, I used the version of the data where these features were deleted.

Interview guides (one for researchers and one for REB members) were prepared ahead of time. (Appendix III) The questions were formulated mainly at the request of the REB, and were drawn up based on my experience with the outcomes study and on my reading about research ethics. The guides were used minimally at most interviews, particularly in the later ones. (Usually I just glanced through it near the end of the interview, to ensure that I had not missed a relevant topic.) A conceptual framework was deliberately omitted to minimize bias when probing the interviewees, although my work with the outcomes study did serve as a starting point. Grounded theorists do not agree about the appropriate timing for the literature review and the building of a theoretical framework. Charmaz comments that while interview guides are not necessary for the methodology, many researchers have to prepare some framework in order to get their work funded and that interview guides can be helpful especially for beginners if the questions are open-ended.

Strauss and Corbin, while they caution that going to the literature too early may have a stifling
effect on creativity and ability to generate new insights about the data, also note that some framing is necessary to know how to listen to the data. I used my experience with the SARS outcome study to develop interview guides, but I had limited understanding of the structure and stresses of an REB. Thus, I felt that I would not be able to force my data with predetermined ideas. After the first three interviews, I began to build diagrams of emerging concepts and had these diagrams with me during the later interviews. I referenced these models, which then served as my emerging conceptual framework, much more often than the interview guides. (See Appendix IV for a series of diagrammatic models.)

15.25 Data Collection - Permanent REB Records

On this second reading of the permanent records of SARS submissions, I did not use a pre-determined data collection form, but rather wrote memos about each protocol, particularly about the recorded interactions between the researcher and the REB and between the REB and public health officials. I evaluated the information from a new and different perspective based on my analysis of the interview data that I had collected to that point. I jotted down anything that seemed interesting in the form of a memo about each file. These memos became my data source for this information.

15.26 Data Collection - Timeline

The first three interviews were conducted from mid-December 2006 to mid-January 2007. Over the next three months, I performed in-depth analysis of these three transcripts and generated my first conceptual models (see Appendix IV for model progression). The fourth interview took place in April 2007, with subsequent interviews carried out over the next eight months. There
was usually a two to three week gap between interviews, which allowed for coding of an interview before the next one took place and for questions that arose from the analysis of one interview to be asked of the next participant. It also allowed me to confirm aspects of my model with the next interviewee. By the end of 2007, I had completed all interviews. Interviews ranged in length from 14 minutes to 81 minutes for a total of 741 minutes and were transcribed onto about 280 pages. The permanent records of SARS-related protocols were re-read in April 2008.

15.27 Analysis

Grounded theory data analysis procedures were used to analyze the transcribed interviews, the information from the re-read of the permanent REB files, and the memos that I had written about them.\textsuperscript{136,179} Using grounded theory, one asks questions of the data and makes comparisons. It has been called a constant comparative method\textsuperscript{182}, because data points, codes, categories and emerging theories are compared, scrutinized and retained or rejected. I began with the method as represented by Strauss and Corbin, but switched to the process as delineated by Charmaz for the reasons described below.

Grounded theory analysis, as it is described by Strauss & Corbin involves three discrete coding steps: open coding, axial coding and selective coding. Coding begins with line-by-line or phrase-by-phrase examination and naming of concepts and processes. The phrase-by-phrase microanalysis (open coding) is especially important in earlier interviews to give direction to subsequent discussions. Open coding is defined as “an analytic process through which concepts are identified and their properties and dimensions are discovered in the data”.\textsuperscript{179} In order to be very familiar with the data, transcripts of the interviews were read through multiple times.
The next step is to look for relationships between and among the emerging concepts and processes and to develop categories of concepts from these relationships. This results in a smaller, more manageable, number of categories, many with multiple sub-categories. This axial coding is defined as “the process of relating categories to their subcategories, and ... links categories at the level of properties and dimensions” \(^{179}\). For example, I had a category called public health/clinician-researcher interaction. It had several properties and dimensions including antibiotics (which ones were being used and whether they were working) and infection control measures (whether they were being used and were there enough supplies for effective use). Using these two types of coding, properties and dimensions of these categories are described and theory building begins. I looked for relationships between categories and subcategories. When inconsistencies arise in subsequent interviews i.e., where the theory didn’t quite accommodate the data, the earlier data are questioned further. This is the third type of coding – selective coding – where integration and refinement of the theory take place. When new evidence seems contradictory, the theory is reworked. Sometimes new information fits the categories described, but is at the extreme range and as such has not been encountered before. Diagrammatic representations of the emerging theory are a useful aid to this process and I used them extensively. They are a visual display of how one’s thinking is evolving at every stage (see appendix IV for diagrams at several stages). I brought the working version with me into the interview rooms where I was able to see the relevance of a particular point and to delve more thoroughly into what was being said. Once a theoretical overview is outlined, it is reviewed. Gaps in logic are resolved, poorly developed categories are expanded, and the scheme is validated. The validation process involves both revisiting the earlier transcripts and asking the next interviewee to clarify emerging concepts and to fill in deficiencies.
About half way through my interviews, I was finding it difficult to move beyond rich description to theory development and became aware of Charmaz’s newly published work on grounded theory. Her approach is less formulaic than that of Strauss and Corbin, but still offers practical advice about how to conduct a successful grounded theory inquiry. Charmaz goes back to the earlier work by Glaser and Strauss, and discusses grounded theory in the context of constructive interpretivism. She agrees with Glaser that axial coding may limit one’s intuition in coding and force one’s thinking into preset frameworks of why, what, how come and what happens as a result of the categories. Charmaz uses initial coding (similar to open coding) and focused coding (making decisions about which initial codes make “the most analytic sense to categorize the data incisively and completely”). She then develops theoretical codes which are integrative and lend form to the focused codes that have been collected to this point. I found her method very helpful and realized that I was being challenged by axial coding. I began to focus more clearly on theoretical codes and was able to move into theory development and away from rich descriptions. Kendall describes a similar problem in her work. She feels that she was led away from her original question by axial coding, and while these results were not ‘wrong’ they were not as meaningful as they might have been. Years after the initial analysis, she returned to her data, re-analyzed it and found more meaning in the theories that she was then able to develop using Charmaz’s method. It is possible however, that she had accumulated more experience with the method and had developed a more sensitive ‘ear’ to the full depth of what the data were saying.
I coded the first three interviews using the tool NVivo (QSR Limited version 2). During this early analysis I generated about 100 codes. Many of these were descriptive and not concepts. A diagrammatic framework, my first attempt at selective coding, was constructed. In the late spring of 2007, I conducted four more interviews, and these were coded and integrated into my theory using NVivo. About this time, I began to feel limited in the ability of the NVivo software to help me move the analysis forward. I had about 125 codes, but was having trouble with axial coding, i.e., grouping codes into categories and sub-categories. In August 2007, I purchased Atlas.ti (version 5.2.0) and transferred all my data into this format. I used Atlas.ti for all subsequent analysis, which I found facilitated coding.

15.28 Rigour

It is important for researchers and readers to evaluate whether there has been appropriate rigour in the development of the theory. In the early 1980's, Lincoln and Guba used the word ‘trustworthiness’ to apply to what is called reliability and validity in quantitative studies. They outlined four components to trustworthiness: credibility, transferability, dependability and confirmability, and proposed some strategies to demonstrate these. Many authors have written on this subject since that time and there is currently no consensus on strategies that are useful across qualitative methods. Charmaz lists four criteria for evaluation of grounded theory studies: credibility, originality, resonance, and usefulness. Different results may arise from these evaluations depending on who is evaluating the work and for what purpose. Morse et al. comment that all of these strategies are conducted post hoc and suggest that if one waits to the end of the study to evaluate rigour, there is little opportunity to correct errors that have occurred along the way. They suggest a process of verification – not in the sense of verifying a theory that
has been already proposed – but a process of “checking, confirming, making sure and being certain” of one’s data and one’s theory as the analysis is unfolding. This is ideally suited to grounded theory as these processes are part of the ‘constant comparative method’ that is the cornerstone of grounded theory.

The first method that Morse et al. espouse is ‘investigator responsiveness’. Grounded theorists are also entreated to be responsive to their data, trying out ideas and rejecting them if they do not fit subsequent data, and looking through the data to make the theory richer, i.e., staying close to the data. Related to this idea is reflexivity, a strategy that is considered to be very important by many qualitative researchers. Charmaz defines reflexivity as: “the researcher’s scrutiny of his or her research experience, decisions and interpretations in ways that bring the researcher into the process and allow the reader to assess how and to what extent the researcher’s interests, positions, and assumptions influenced the inquiry.” In order for a reader to be able to evaluate this, there must be a statement in the report about the researcher and what assumptions and biases s/he might bring to the research. I have included such a statement at the beginning of this thesis.

The second method that Morse et al. discuss is ‘methodologic coherence’ or matching the question to the method used. The strategy of pairing the method of inquiry to the question posed is one area where qualitative and quantitative research methodologists agree. My question of ‘What were the issues, and how were they managed’ seemed ideally suited to a grounded theory inquiry. Little was known or documented about the process of research ethics review during a public emergency, and talking to the people who were involved with the process was the best way to discover what had occurred during this time. Grounded theory helped me to delve
into the data and to formulate a theory about the impact of SARS on research ethics boards. This raised the analysis above the level of comprehensive description.

Choosing an appropriate sample is the third method that Morse et al. discuss. This is required to ensure that appropriate insights are sought to allow the emergence of meaningful categories and to fully saturate them. In order to discover what had occurred with research ethics review during the SARS outbreak, I spoke with those who had submitted protocols to the REB and also to those who had reviewed them. Adequacy of sample size also falls into this category. I interviewed nineteen individuals and while I would have liked to interview several other individuals, particularly from the community hospital, these were not available to me as described above. However, I did feel after going back repeatedly to my data in the analysis, that my categories were saturated, while again acknowledging the limitations in recruitment outlined earlier.

Collecting and analyzing data concurrently is an important aspect of grounded theory, and it is the fourth method that Morse et al. put forth. Each interview that I performed was coded as soon as I received the transcript back from the transcriber and some analysis was done. Larger analytic efforts were undertaken after three, seven, ten, fifteen, and after all nineteen interviews were completed. At each of these points, my analytic model was modified as I tried out various visual representations of my data. Morse et al. propose thinking theoretically and developing a theory as the last steps in ensuring rigour. These steps are inherent in the process of grounded theory.

Many of the above methods are explicitly part of grounded theory. Strauss and Corbin include a table of the characteristics of a grounded theorist:

1. The ability to step back and critically analyze situations
2. The ability to recognize the tendency toward bias
3. The ability to think abstractly
4. The ability to be flexible and open to helpful criticism
5. Sensitivity to the words and actions of the respondents
6. A sense of absorption and devotion to the work process

I strove to achieve these characteristics and felt that I had used the strategies described by Morse et al. to ensure rigour.

Peer debriefing was one further strategy that I used to ensure rigorous results in my study of research ethics review during the SARS outbreak. A small group of student grounded theorists was organized and we reviewed each others’ emerging theories on several occasions. I also gave several talks and poster presentations which helped me to think through the evolving ideas and provided excellent feedback for me to pursue in my analysis. Many formal and informal meetings occurred during which both of my supervisors, Drs. Lavery and Herridge, and I brainstormed about my findings. These sessions were enormously helpful to me in the formulation of my theory.

15.29 Confidentiality

Tapes of the interviews for the qualitative study and consent forms that the participants signed were kept in a locked cabinet in a locked area of the hospital. The transcriber used a secure web site to transmit audio files and Word transcripts, and individuals’ names were deleted from written documents. Although only initials were used from that time forward, someone who was familiar with the institutions studied might still be able to identify certain key individuals.

In my presentations and writings about this project, I have taken several steps to make it more difficult to identify my research participants. This is important since the infectious disease (ID) and the research ethics review communities in Toronto are small. First, I do not identify the
two hospitals from which I drew subjects; therefore I have not appended the letters of approval received from their REBs to this document. Second, I speak of all the interviewees as being female, although some of them are male. Third, I only identify people by their study number and not by initials or by their job title or description. Despite these efforts, however, anyone who knows these communities may be able to identify some of the individuals who were interviewed.

Academics require freedom to publish their works, but also have a duty to do so. It can be argued that in this study, even if individuals are identified, there is little harm that will ensue to the participant particularly given the time that has elapsed since the SARS outbreak. The risk of being identified was detailed in the consent form that all participants read and signed. At least two people stated in their interviews that they did not want to expound on a particular topic, and I did not ask for details.

15.30 Risk to Interviewees

Two further risks to interviewees are outlined in the consent form that was read and signed by each interviewee. These are 1) that interviewees might find it difficult to relive the difficulties during the SARS outbreak and 2) that I might discover some evidence of wrong-doing. The first was mitigated by telling participants that all participation was voluntary and that the interview could be stopped at any time if the interviewee so wished or s/he could refuse to answer a particular question. I told interviewees in the consent form that if I discovered evidence of serious wrong-doings of a legal or ethical nature, I would bring this evidence to the attention of my thesis advisory committee to determine the appropriate action. This never occurred.
CHAPTER 16: ‘TWO REBS’: RESULTS & DISCUSSION

In this chapter, I report on the results of the file review of the two REBs. The objective of the file review was to determine the type and number of research projects submitted for research ethics review during the SARS outbreak and to document the time from submission to completion of the review. First, I discuss some details about each of the REBs before the SARS outbreak to provide context. This information was provided to me by the ethics coordinators at each site as part of the file reviews. Then, I provide descriptions of the protocols submitted to the two REBs including who was studied and the REB time to approval. I further explore details about the timing and characteristics of the protocols in the subsequent section. Lastly, there is discussion of the results from this small study, its limitations and the conclusions that I draw from this file review.

16.1 Background about the Two REBs before the SARS Outbreak

The first REB that I reviewed is that of a large urban community hospital that was one of the epicentres of the SARS outbreak in Toronto. The focus is community medicine and clinical care and not research. In 2003, this REB was staffed by one individual who performed the roles of administrative assistant of the REB as well as REB coordinator, data manager and research assistant. (called ethics coordinator hereon in for simplicity) and it was from this person that I obtained background information. The REB meets once a month and in 2002 reviewed 35 protocols, of which only four were expedited. Ten protocols were industry sponsored. Researchers are invited to REB meetings to answer questions about their protocols, but do not
remain in the room while the REB members discuss the protocol. Every protocol that is submitted with a consent form is sent to the full REB for review. Resident trainees’ protocols (whether submitted with a consent form or not and whether eligible for expedited review) are also sent to the full REB as the chair feels that the presentation to the REB provides an educational experience for these trainees. Most approved research projects are complete within one year, but when a renewal is required, it is sent to the full REB. Expedited review is conducted by a team of three people – the hospital ethicist, the chair of the REB and the research manager.

The second research ethics board that I reviewed is that of a large urban academic research centre. There are three meetings each month attended by different REB members; all meetings are presided over by the same chair. At one of these meetings, only oncology protocols are reviewed. In 2002, the REB office was staffed by three research ethics coordinators and 886 protocols were reviewed, of which 444 were expedited. Non-oncology researchers are rarely called to an REB meeting, although there may be phone or e-mail contact before and/or after the meeting either with the chair or with the ethics coordinator assigned to the protocol. The decision to send a proposal to the full REB or to review it in an expedited fashion is made by the ethics coordinators who consult with each other and with the chair if they have concerns. Expedited review is conducted by a research ethics coordinator in consultation with the chair, who signs the letter to the investigator once s/he is satisfied that the review is complete.

16.2 Description of Protocols Submitted to the Two REBs during the SARS Outbreak

There were twenty-eight SARS-related protocols submitted in 2003 at the academic centre. At the community hospital, it was difficult to determine how to count the submissions, as
the computer record and the paper files did not exactly match. There were three protocols on the computerized list that were not formally reviewed. Two protocols, filed as three separate submissions, appeared to be part of a single large complicated project. I have counted the submissions to the community hospital as seven (SARS-07, SARS-02, SARS-08, SARS-02x, SARS-06, SARS-10, SARS-11) as described below. Details about these protocols are listed in Table 16.1. The protocol numbers that I assigned to them are listed in the first column labeled ‘My study #’; those with a suffix of ‘a’ are those submitted to the academic centre and those with a ‘c’ suffix were submitted to the community hospital; therefore protocols with both suffixes (e.g., 3a/1c) were submitted to both institutions. As described in the methods section, protocols were sorted into categories according to who was eligible to participate in the study 1) HCW: those involving health care workers, 2) patients: those involving SARS patients, their radiographs, tissues or blood samples, and 3) non-SARS patients and 4) healthy volunteers. I have also highlighted studies about the psychological or social impact of the outbreak.

<table>
<thead>
<tr>
<th>my study #</th>
<th>Community hospital #</th>
<th>Description of Protocol</th>
<th>time from submission to approval (days)</th>
<th>Category*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>academic</td>
<td>community</td>
</tr>
<tr>
<td>nr1§</td>
<td>SARS-01</td>
<td>not reviewed - no file</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1a†</td>
<td>SARS-07</td>
<td>ribavirin treatment trial no paper records kept at community hospital</td>
<td>1</td>
<td>patients</td>
</tr>
<tr>
<td>2a</td>
<td></td>
<td>gene expression profiling &amp; protein expression profiling in SARS patients</td>
<td>0</td>
<td>patients</td>
</tr>
<tr>
<td>3a/1c‡</td>
<td>SARS-02</td>
<td>chart review – natural history of the disease</td>
<td>-3</td>
<td>2</td>
</tr>
<tr>
<td>my study #</td>
<td>Community hospital #</td>
<td>Description of Protocol</td>
<td>time from submission to approval (days)</td>
<td>Category*</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>academic</td>
<td>community</td>
</tr>
<tr>
<td>4a</td>
<td>Community hospital</td>
<td>quality of life in SARS</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>patients 2 weeks after</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>diagnosis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5a</td>
<td>Community hospital</td>
<td>phenomenological -</td>
<td>11</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>persevering through a</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>difficult time</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6a</td>
<td>Community hospital</td>
<td>T cell mapping in SARS</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>convalescent patients</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>(overlaps with CSRN?)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>7a</td>
<td>Community hospital</td>
<td>characterization of ICU</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>patients</td>
<td></td>
<td></td>
</tr>
<tr>
<td>8a</td>
<td>Community hospital</td>
<td>aural thermometer</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>assessment</td>
<td></td>
<td></td>
</tr>
<tr>
<td>9a/4c</td>
<td>Community hospital</td>
<td>positive seroprevalence</td>
<td>7</td>
<td>14</td>
</tr>
<tr>
<td></td>
<td>SARS-08</td>
<td>of SARS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>10a</td>
<td>Community hospital</td>
<td>difficult intubation</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>management questionnaire</td>
<td></td>
<td></td>
</tr>
<tr>
<td>11a</td>
<td>Community hospital</td>
<td>qualitative impact of</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>being quarantined</td>
<td></td>
<td></td>
</tr>
<tr>
<td>12a</td>
<td>Community hospital</td>
<td>impact of outbreak on</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>house staff</td>
<td></td>
<td></td>
</tr>
<tr>
<td>13a</td>
<td>Community hospital</td>
<td>expression of fg12 in</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>SARS tissue</td>
<td></td>
<td></td>
</tr>
<tr>
<td>14a/2c</td>
<td>Community hospital</td>
<td>CSRN studies (see</td>
<td>1</td>
<td>34</td>
</tr>
<tr>
<td></td>
<td>SARS-02x</td>
<td>previous chapters</td>
<td></td>
<td></td>
</tr>
<tr>
<td>15a</td>
<td>Community hospital</td>
<td>HCW perception of risk</td>
<td>9</td>
<td></td>
</tr>
<tr>
<td>16a</td>
<td>Community hospital</td>
<td>priority setting</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>17a</td>
<td>Community hospital</td>
<td>quarantine study</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>my study #</td>
<td>Community hospital #</td>
<td>Description of Protocol</td>
<td>time from submission to approval (days)</td>
<td>Category*</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>academic</td>
<td>community</td>
</tr>
<tr>
<td>18a</td>
<td></td>
<td>information seeking in new oncology patients</td>
<td>50</td>
<td></td>
</tr>
<tr>
<td>19a</td>
<td></td>
<td>impact of attending a conference</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>20a</td>
<td></td>
<td>viral RNA, cytokine expression in interferon treated patients</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>nr2</td>
<td></td>
<td>interferon treatment (submitted in case of need)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>23a</td>
<td></td>
<td>evaluation of management of SARS outbreak</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>24a</td>
<td></td>
<td>impact of SARS on social workers</td>
<td>24</td>
<td></td>
</tr>
<tr>
<td>nr3</td>
<td></td>
<td>impact of the outbreak on provision of continuing medical education credits</td>
<td></td>
<td></td>
</tr>
<tr>
<td>25a</td>
<td></td>
<td>impact of the infection control measures on newly diagnosed oncology patients</td>
<td>11</td>
<td></td>
</tr>
<tr>
<td>nr4</td>
<td>SARS-04</td>
<td>no information in the files</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3c</td>
<td>SARS-06</td>
<td>radiologic pattern of disease</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td></td>
<td>SARS-09</td>
<td>intubation study - public health withdrew the study, so it was not reviewed by the REB</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5c</td>
<td>SARS-10</td>
<td>effect of SARS on emergency department usage</td>
<td>43</td>
<td></td>
</tr>
<tr>
<td>6c</td>
<td>SARS-11</td>
<td>the lived experience</td>
<td>26</td>
<td></td>
</tr>
</tbody>
</table>
Table 16.1 SARS-Related Protocols Submitted to the Two REBs

| Study # | Community hospital # | Description of Protocol | time from submission to approval (days) | Category*
|--------|-----------------------|-------------------------|----------------------------------------|-----------------
|        |                       |                         | academic                               | community       |
|        |                       | mean time from submission to approval (days) | Academic | 7 | 21 |
|        |                       | median                  | Community | 4 | 20 |
|        |                       | range                   |          | -2 to 50 | 2 to 43 |

* Categories are based on participants eligible: 1) HCW = involve health care workers and 2) SARS patients = involve SARS patients their radiographs, tissues or blood samples, 3) non-SARS patients and 4) healthy volunteers. Also categorized according to impact studies (examining the psychological or social impact of the outbreak) or not.
† a in the protocol numbers refers to proposals submitted to the academic centre REB
‡ c in the protocol numbers refers to proposals submitted to the community hospital REB
§ nr refers to not reviewed

16.21 Protocols Submitted to the Community Hospital REB

Protocols that were submitted to the community hospital REB during the SARS outbreak were given file numbers prefixed with ‘SARS’. This designation was made by the staff of the REB and it is these files that I reviewed at this hospital. File numbers ran from SARS-01 to SARS-14, but SARS 12, 13 and 14 were submitted after the end of 2003 and were not considered in this file review since they were submitted so long after the emergency. Some numbers were not used and number 2 (SARS-02 and SARS-02x in the table) was duplicated. Why this occurred is not clear. Based on the material that I was given, there were ten SARS-related protocols submitted to the community hospital REB in 2003 of which six were reviewed and approved. A seventh protocol was reviewed and not approved. This protocol was that of a proposed treatment randomized controlled trial that was not undertaken at any centre in Toronto as Health Canada withdrew the letter of ‘no objection’. Details about REBs and this trial have been published.65
Two more submissions were not reviewed, no paper charts were kept and so I have no details about these. Another proposal that was submitted but not reviewed by the REB was withdrawn when senior public health officials deemed this project to be outbreak investigation and thus not within the purview of the REB. The mean time from submission to approval was 21 days (median 20 days; range 2 to 43 days). Only one protocol was expedited (3c). External funding was awarded in only one of the protocols (2c) approved at the community hospital. No details about the process of review were kept within the files.

16.22 Protocols Submitted to the Academic Centre REB

A computerized database of all REB submissions is maintained by the academic centre REB. I searched for the word ‘SARS’ in the title of all protocols submitted between January and December of 2003 and retrieved twenty-seven SARS-related protocols. One further protocol without SARS in the title was also examined. All but two of the twenty-eight SARS-related protocols were reviewed by the REB and approved. One protocol (not numbered in Table 16.1) had no details other than the title and the researcher’s name listed in the computer file and no paper file was found. Thus it was unclear if this submission was ever made. One protocol was not approved as the investigator did not respond to the queries and clarifications requested by the REB. The complete list of SARS-related protocols submitted to the academic centre is presented in Table 16.1. Time from submission to approval was shorter than that at the community hospital – a mean of 7 days (median 4 days; range -2 to 50 days). All but one of the protocols received expedited review, which was carried out by one of the ethics coordinators in consultation with the chair of the REB. Notes from both the ethics coordinator and the chair were found in the files. No details about the nature of the review of a proposed treatment trial were found in the file.
External funding was awarded in four protocols submitted to the academic centre (6a, 14a, 16a, 21a).

1.6.3 Timing and Characteristics of Protocols

The first submissions were received at each of the REB offices about one month after the presentation of the first case of SARS in Toronto and about two weeks following the first large influx in cases which occurred in mid-March 2003. Most protocols were received over the next two months (April – May 2003), and submission rates waned quickly once new cases were no longer occurring.

Twenty-eight protocols were approved between the two REBs (3 at both centres). The protocols submitted to the two REBs studied health care workers (HCW) (13 proposals), SARS patients or their radiographs or used tissue or blood samples from those affected (10 proposals), non-SARS patients, their families and HCW (1 proposal), healthy volunteers (1 proposal), oncology patients (2 proposal) and emergency department usage (1 proposal). The protocols that involved HCW looked at impact on social, psychological or practice patterns (6c, 5a, 11a, 12a, 17a, 19a, 24a), effectiveness and impact of infection control measures (8a, 10a, 15a, 21a, 23a), transmission patterns (9a/4c) or priority setting (16a). Two of the protocols that were deemed to be public health surveillance (SARS-04 and 09) also involved questioning HCW. Eleven studies
(6c, 4a, 5a, 11a, 12a, 15a, 17a, 18a, 19a, 24a, 25a) investigated psycho-social impact and enrolled differing combinations of patients and their families, community members and healthcare workers. One further study (5c) explored the impact of the outbreak on the emergency department usage. Figure 16.1 depicts the type of participants in the impact studies. Of the ten proposals that involved SARS patients, four were basic science protocols using patient tissue samples (2a, 6a, 13a, 20a), two were randomized control trials of treatment that never took place (1a/SARS-07, 23a), one was a quality of life study (4a), one was a longitudinal study with basic science and quality of life (QOL) components (14a/2c), two were retrospective chart reviews (3a/1c, 7a) and one looked at radiologic pattern of disease (3c).

Many protocols were submitted to each centre. However, their impact on the REB may not have been the same. At the community hospital, the number of SARS-related protocols received in 2003 was equal to 20% of the previous year’s submissions. Once the Code Orange (external disaster with mass casualties) was declared by the provincial government, the REB at the community hospital was closed and most staff were seconded to other posts. Only the
protocols deemed by the REB to be SARS-related were reviewed. The REB at the academic centre never closed and continued to review non-SARS proposals as time allowed after SARS-related protocols had been dealt with. All but one of the SARS-related protocols was reviewed using an expedited or delegated process. The twenty-eight SARS proposals that were submitted were only equal to 3% of the previous year’s volume at the academic centre.

As can be seen from table 16.1 above, there is some overlap in the proposals submitted to the two centres; three protocols (1c/3a; 2c/14a; 4c/9a) of the six (50%) that were approved at the community hospital, and four (1a/SARS-07; 3a/1c; 9a/4c; 14a/2c) of the twenty-five (16%) that were approved at the academic research centre were submitted to both REBs. Since submission to other REBs is one of the questions on the required REB submission form at both REBs, I knew that all four protocols were also submitted to other REBs across the greater Toronto area. One protocol (1a/SARS-07) submitted to both centres was approved at the academic centre (although not carried out), but not at the community hospital. Despite the approval at the academic centre, this proposed randomized controlled trial (RCT) was not conducted since Health Canada withdrew its approval and some key study team members were quarantined or fell ill with SARS. In total, there were twenty-eight unique protocols submitted to the two centres. As expected, few (two) of the protocols that were submitted to the community hospital had a principal investigator (PI) who was affiliated with their institution. These two protocols were the last two submitted to the community hospital (June 5 & Sept 18). The lack of a research focus at the community hospital may be a factor in the preponderance of PIs from academic centres.

The file review at the academic centre revealed that there were eighty-two principal and co-investigators on the SARS studies submitted for REB approval, but only two people who were primarily involved with reviewing the proposed research. At the community hospital, there were
twenty-eight investigators listed on SARS protocols, and twenty-one individuals listed as having reviewed these projects. The academic centre may have perceived the influx of SARS-related protocols (3% above last year’s volume as opposed to 20% increase in volume) to be less daunting than did the REB at the community hospital as was reflected in the fact that it was able to continue to process some other submissions.

16.4 Discussion about the ‘Two REBs’ Study

I learned five things from the file review. First, I learned that expedited review was defined and operationalized differently at each of the two institutions. Second, I discovered that health care workers were the participants of interest in nearly half of the proposed studies and may have become a vulnerable population. Third, I found that most of the studies submitted to the REBs were internally funded. Fourth, I learned that one proposed treatment trial submitted to both REBs that I reviewed was approved at one and not at the other. Finally, I understood that the interaction between the REB and public health, particularly at the community hospital was antagonistic. Each of these findings is discussed in more detail below.

A critical difference between the two REBs was how each REB defined expedited review both before and during the SARS outbreak. As mandated by the TCPS and described above, each review begins with “an assessment, primarily from the viewpoint of the potential subjects, of the character, magnitude and probability of potential harms inherent in the research.” However, one board assigned almost all protocols to expedited review and the other assigned almost all protocols to the equivalent of full board review as it was operationalized during the outbreak. Inconsistencies involving different types of review boards studies under normal circumstances is well documented in the research ethics literature. I demonstrated that this disparity of
review process also occurs under emergency situations. Prior to the SARS outbreak, each of these institutions had very different definitions of which proposals qualified for expedited review and thus it is not unexpected that this would continue in an emergency. I was unable to tell from the file review how each board determined eligibility for expedited review during the outbreak.

Health care workers (HCW) were perhaps one of the most vulnerable groups of research participants during the SARS outbreak. While SARS patients were also a vulnerable group, there were just two studies (14a/2c, 4a) where patients were interviewed or examined. Perhaps this reflects the priority placed on basic science questions before formulating more complex protocols that required this knowledge base. Patient studies are difficult to implement in the context of an outbreak and are the most likely to result in harm to research staff (infection with the virus). In contrast to the low number of studies enrolling SARS patients, there were fourteen studies that recruited HCW. HCW were also questioned by public health officials in their outbreak investigations and many HCW became ill and therefore were also eligible for patient or treatment-related studies. This may have raised concern by REBs about whether HCW were at risk of being overburdened from multiple studies. I was unable to tell from the file review if this aspect of HCW participation in research protocols was discussed by REB members.

HCW might also have been more vulnerable to pressure to participate in research that was conducted by their colleagues. While this may not have been overt, there may have been a perception of pressure to participate on the part of HCW. HCW see the advances made by medical science everyday in their work. They know that they are only made possible by the past participation of research subjects. Because of this, they may feel obliged to do their part in medical research. This is the free rider argument as it is discussed by Harris and described in this thesis in the earlier section on social obligation to participate in research. To my knowledge,
no attempt was made to understand how participation in research was viewed by those HCW that
did opt to take part in SARS-related research projects. One wonders: did they feel free to say no?,
did they feel a social obligation to participate?, did they feel pressure from co-workers to
participate?, did they feel pressure from PIs and Co-Is, who may have been their co-workers?
None of these questions has been answered.

Because internally funded studies are less likely to have undergone a formal peer review,
REBs may want to scrutinize these protocols carefully for scientific value and validity. Many of
the submitted SARS-related protocols were funded with monies from sources internal to the
hospital of the investigator. Thus formal evaluation of the scientific value and validity by
scientists not affiliated with the proposed work may not have occurred. A similar situation arose
with respect to funding after the Oklahoma bombing disaster. Quick points out that many of the
studies approved by the University of Oklahoma Institutional Review Board after the bombing
were internally funded. 64 However, the circumstances of the emergency and the unknown
elements in battling a contagious and novel pathogen make assessment of risk difficult. I argue
that because of this difficulty, peer review is more important than under normal circumstances.
When peer review has not occurred prior to REB review, it falls to the REB to “review the ethical
implications of the methods and design of the research” 16. A strategy to deal with this is put forth
in part IV of this thesis.

One of the projects (1a/SARS-07) reviewed at both centres was approved at the academic
centre, but not at the community hospital. This proposed ribavirin treatment trial for SARS
patients was perhaps the highest risk protocol submitted to either REB. As discussed above,
investigators used reasoning by analogy and so ribavirin was chosen for the treatment of SARS
based on its broad-spectrum antiviral activity. 198 The trial involved risk to patients as there was
little science about the pathogen on which to base dosage, route of administration of the drug and length of treatment decisions, although there was knowledge about the drug for other indications. The considerable toxicity pattern of ribavirin was also known. Muller et al. describe many of the special difficulties that the researchers encountered because of the lack of experience with the virus as they developed this protocol. As discussed earlier, these include identifying the study population, defining the intervention, defining the outcomes, and recruiting participants. I was unable to discern which of these factors was important in the community hospital’s decision not to approve this protocol as there were no details kept in the file. Similarly, I had no insight into what factors prompted the academic hospital to approve the project. The only method that would give me a fuller appreciation of the nuances of the events was to talk to the individuals involved.

The proposed ribivirin trial also involved risk to research workers. Infection control measures were evolving and not always effective. While the World Trade Center attacks did not involve an infectious agent, Qureshi and her colleagues proposed several strategies to protect research staff which included training appropriate to the disaster and the research proposal, regularly scheduled support meetings with co-workers and access to psycho-social counselling if required. The TCPS (both current and revised editions) does not offer guidance on investigators’ obligation to protect their research staff. During the SARS outbreak, many health care workers became ill from the virus and research staff were equally at risk when they interacted with SARS research participants in the infectious stages of the illness. While the purpose of the TCPS is to provide guidance about protection of research participants, during a public emergency the risk to research staff may be greater than usual. As such, the document might be strengthened if this gap was addressed in a further revision particularly in the section concerning public emergencies.
Another area of difference between the experiences of these two REBs is their interaction with the public health authorities. Several protocols were submitted to the community hospital, and then withdrawn when senior public health officials designated the protocols to be outbreak investigation and so not subject to REB authority. This did not occur at the academic centre, perhaps because the community hospital was an epicentre of the outbreak and the academic centre was not. From the paper files, I was not able to get an understanding of the dynamics of these interactions. While public health officials did not report on their interaction with particular hospitals in their discussions with me, they did articulate their strongly held views about what is research and what is routine public health practice in the context of an infectious disease outbreak. Their views and their implications are reported in Chapter 17.

16.5 Limitations of the ‘Two REBs’ Study

This small study is limited in its ability to provide the type of information that I was seeking. Many details about the reviews are not discernable with this study design e.g., I was unable to tell how each board defined expedited review during the outbreak, although I had some information about how it was defined under normal circumstances. I could not tell what factors were important in the community hospital’s decision not to approve the ribivirin trial nor what issues had been discussed by the academic hospital’s REB. At the end of this study, I had little insight into the review process and how it changed at each institution because of the outbreak. I was not able to gain an understanding of the nature of the interactions between the public health officials who submitted research protocols to the community hospital and its REB. All of these questions require a more in-depth inquiry into the operations of the REBs. A different methodology was required. I decided that the best way to understand these issues was to speak
with the people involved and so developed the qualitative study that is described in chapters 15 and 17.

16.6 Conclusions of the ‘Two REBs’ Study

As discussed above, despite limitations of the small size of the study, I was able to learn some details about the operation of the two REBs. In particular, I learned how each REB defined expedited review under normal circumstances, and that health care workers were often the subjects of interest in the studies submitted. I also became aware that most of the studies were internally funded and therefore had not undergone the rigour of peer-review and that one treatment trial was approved at one of the centres and not at the other using criteria that were not wholly transparent.
I concluded the previous chapter by highlighting the fact that the REB file review was limited in its ability to reveal insights needed to understand the impact of the SARS outbreak on research ethics review of SARS-related protocols. I did not understand the stressors that were felt by REBs as a result of the outbreak, the responses to these stressors or the interaction between the various players in particular between REBs and public health officials. As a result of this I undertook the ‘Three Solitudes’ study described in Chapter 15 and the results are described in this chapter. The objective of the ‘Three Solitudes’ study is to build a theory about the impact of the SARS outbreak on the research ethics review system as it processed SARS-related protocols submitted for REB review. My primary data source for this inquiry was verbatim-transcribed records of semi-structured interviews with researchers, REB members and public health officials who played an active role in the research that was carried out during the SARS outbreak. A secondary data source was the permanent records maintained at the REBs of both institutions that I studied in the ‘Two REBs’ reported in the previous chapter. Throughout this chapter, R is the respondent and I is the interviewer in the quotes from the participants.

17.1 The Interviewees

My sample included 19 informants/interviewees:
- 2 academic centre REB members
- 3 community hospital REB members (one of whom also conducted a research project about SARS)
- 4 academic researchers only at the academic centre
- 6 academic researchers who conducted research at both the community hospital and the academic centre
- 1 academic centre infection control physician
- 1 community hospital infectious disease physician
- 2 public health physicians (both with academic affiliations)

Further demographic details about these people are not provided for two reasons. First, it would not contribute to the understanding of the theory and second because with the small infectious disease and research ethics review communities, this could reveal the identities of these individuals. Similarly, to enhance their privacy, I speak of all the interviewees as being female, although some of them are male.

17.2 The Theory

In this section I provide an introductory overview of the theory that was developed as a result of the grounded theory inquiry. It is a theory about the stressors that affected research ethics boards, the players involved in this process, how each of these players responded to the SARS outbreak and the interaction between them. I describe the theory in greater detail throughout this chapter. The purpose of this overview is to provide orientation about the relevant players, concepts and the inter-relationships among them and a framework for the detailed account that follows. I begin by defining all terms used in the schematic of the theory. I then describe what I mean by the various colors, boxes, dotted and solid lines that are depicted in Figure 17.1.
The SARS box represents the outbreak of severe acute respiratory syndrome that occurred in Toronto beginning in March 2003. The players in my theory are researchers, public health and REBs and are displayed in blue; these are the ‘Three Solitudes’. Researchers and Public Health are in both blue and green since they are both players as well as stressors on the REB as discussed below. REBs refers to the two REBs that I reported on in the previous chapter i.e., one academic centre and one community hospital. Both institutions had cared for SARS patients and were staffed by investigators who were interested in studying some aspect of the SARS outbreak. The community centre was one of the two epicentres of disease spread. Researchers are those
investigators who submitted proposals to the REBs and conducted a research project(s) once it had been approved by the REB. Public health refers to those individuals within the public health department of Toronto who oversaw and directed the SARS outbreak investigation to understand and stop the spread of the virus. The public health units in Ontario are staffed by associate medical officers of health (physicians) who report to the Ministry of Health and Long-Term Care through a medical officer of health. The data that I present about the operations of the public health office are primarily the perspective of the two physicians whom I interviewed. Stressors on the REB are depicted in green. The stress that was felt by the REBs was mediated by researchers who submitted research protocols that required ethics review, as well as the public health office that submitted protocols. Public health also mandated infection control measures. Thus researchers and public health are represented as both players and stressors. Not depicted on the schema, but certainly felt by individuals REB members was the general stress and fear of the outbreak that was pervasive throughout the city and both hospitals. The black solid lines and boxes depict how each of the players responded to the outbreak. Finally the orange dotted lines (obstruction, manipulation and coercion) show the interactions that occurred among the players.

Complementing this final version of my theory is a series of graphic representations (presented in Appendix IV) of the theory and how it changed as the interviews progressed. This documents the evolution of my grounded theory as I proceeded with analysis and interviews. In particular, it highlights the iterative process of returning to the data and refining the theory using the constant comparative method described in Chapter 15. It provides an opportunity to understand in greater detail the relationship between grounded theory analytic procedures and the evolution of theory.
My interviewees discussed four areas that I found particularly interesting and I focus on them for the remainder of this chapter: 1) what stressors were felt by REBs; 2) how the REBs responded to these stressors; 3) how researchers responded to the outbreak; and 4) how the three groups of interest (REBs, researchers and public health officials) interacted with each other during the outbreak.

17.21 Stressors felt by Research Ethics Boards

In this section, I will discuss three stressors of the two REBs during the SARS outbreak. These are: 1) the infection control measures imposed by public health; 2) the indistinct boundary between public health surveillance/outbreak investigation and research during a public emergency; and 3) pressure applied by some investigators to approve protocols quickly.

![Figure 17.2 Stressors felt by REBs during the SARS outbreak](image-url)
The Impact of Infection Control Measures Imposed by Public Health

In order to control the spread of the SARS virus, the Ministry of Health and Long-Term Care in Ontario declared a public emergency which restricted hospital access to personnel, patients and visitors. Restrictions were implemented in various ways across hospitals, and some of these are outlined below:

Each person entering a hospital was required to:

1) complete a form stating that s/he was feeling well
2) have a normal aural temperature
3) stay at least 3 metres from other staff members while in the hospital
4) declare that s/he had not visited another hospital within the last 10 days

Also:
5) No visitors were allowed on hospital premises
6) Students and volunteers were not permitted into the hospital
7) Non-essential workers were discouraged from entering the hospital (research staff was deemed non-essential)
8) Out-patient clinics were cancelled
9) Elective surgery was cancelled
10) Meetings with more than 3 people were not allowed

Individually, each restriction was not overly onerous, but collectively, they were problematic as REBs attempted to interpret and implement them against the backdrop of the TCPS. In particular, the limits placed on volunteers and research staff entering hospital had an impact on the operations of REBs, as did the limits placed on meeting size. The fact that once an individual had entered one hospital, s/he was not allowed to enter another one made coordination of multi-centre research very difficult. At the community hospital, research was deemed to be non-essential, and thus the REB was closed. These restrictions were discussed by one REB member:

R ... all meetings in the hospital and all committees and all groups were banned. We were... nobody was allowed to meet. We weren’t supposed to congregate, everybody, it was a very surreal time . . . . But anyway that meant the REB was suspended. Also we
couldn’t bring in researchers, and that was something that we often did. We often invited researchers in to discuss their protocols with us. They could no longer come into the hospital. Our community members couldn’t come in to the hospital.

I of course...

R People who were at the one division were not allowed to come to the other division, even if they were out of quarantine, they couldn’t come in, it was very confusing, but anyway, ... not only were we not allowed to hold the REB, but practically speaking the key people could not come to an REB meeting even if we were able to hold one.

Participant #2

Once researchers began to call REBs asking about the procedure to follow for submission of SARS-related protocols, REBs realized that they would quickly have to formulate a procedure to address these requests. They wanted to follow the TCPS as closely as possible while still respecting the infection control measures that were in place. The incompatibilities between the TCPS guidelines and the Ministry of Health and Long-Term Care directives made this difficult.

As mentioned by participant #2 above, community members, who bring an important perspective to REB discussions, were not permitted onto hospital premises and this was problematic because the TCPS explicitly calls for face-to-face discussion. Since the infection control measures were mandated by the Ministry of Health and Long-Term Care, REBs were required to prioritize infection control mandates over the face-to-face REB meeting requirements of the TCPS and therefore teleconferences were used. The infection control restriction that meeting size be kept to three or fewer people was also in direct conflict with one of the guidelines of the TCPS which calls for a minimum of five people on a full research ethics board. The community hospital allowed five or more members to attend their REB meetings in person, but all wore gowns, gloves and masks. In contrast, the academic centre chose a modified expedited format for their meetings using multiple teleconferences for review of protocols that they assessed as being more than minimum risk. In the words of one of the REB members from the academic centre:
R We couldn’t meet face-to-face in a regular sort of meeting because that wasn’t allowed. And so that was an immediate departure from the Tri-Council Policy...
I Right.
R ...approach of going face-to-face, which was hotly debated after that, I guess.
I you mean the prohibition against meeting?
R the prohibition again... or the interpretation that the Tri-Council prohibited anything other than face-to-face meetings...
I Okay... okay.
R Which if you read the language and interpret it strictly, as one might do if you were interpreting the Bible...
I Heh...
R ...you can read it word for word and that’s what it says.
I Right.
R But the interpretation may be something beyond that...
I Right.
R and some of us are not so wedded to the literal translation of what it means. So in the first review of the first protocol which was the intervention protocol that we did, . . . . an ad hoc committee [was struck], by teleconference, including some people from outside Toronto, particularly some people from Hamilton to provide input to the REB on this...and these were experts in the area of infection control.

Participant #3

Thus at both institutions, the rules about the review process were changed – they were forced to change their procedures to achieve a workable solution. In each case, the REB realized that the infection control measures trumped the usual procedures outlined in the TCPS. These changes were made with little or no consultation between REBs. No attempt was made to standardize procedures across the city because of logistical and time constraints. In normal times, there is little communication between REBs from different institutions, although some effort is now being made with the creation of the Toronto Academic Health Services Network (TAHSN), an organization of REBs affiliated with the University of Toronto; this organization does not include the community hospital that I studied. Thus with no clear directives from either internal or external (to the institution) sources, REBs were isolated and left to change their procedures as they saw fit. Infection control measures rendered normal procedures impossible to follow.
17.212 Boundary between Public Health Surveillance/Outbreak Investigation and Research

The distinction between surveillance or outbreak investigation and research was particularly challenging at the community hospital. As was mentioned earlier, two protocols were submitted to the community hospital REB and then retracted (SARS-09 from Table 16.1 and I suspect SARS-04). SARS-09 planned to investigate those factors that potentiated transmission of the virus to health care workers during intubation of SARS patients despite the use of infection control precautions. I do not know the details of SARS-04 as the protocol was not kept by the REB. What transpired at the public health office with respect to these two protocols is unknown. However, SARS-09 was closed by the REB office when a letter was received from the Medical Officer of Health stating that the proposal was part of a public health investigation and was not research. The letter asked for hospital staff to please cooperate with the public health team. This process of submission and then retraction was difficult for both REB members and for public health officials, and highlights the lack of consensus about what is research and what is routine public health practice.

R And, so, we had this huge study, as I said, it was five parts and it included blood tests, and all sorts of interviews and it was... it was... anyway we said no. And then we got a call from Public Health from one of the high up people in Public Health they said... we don’t care what you think. This is a public health investigation - we don’t need your okay.

I What?

R We’re coming in. That’s what we said. Why are you? ... Well then why did you bring it to us, if you think you have the authority to come in and do this, and not... And they said, “Well one of the parts, the phlebotomy study is not really an investigation. So we need you to do that. But forget the rest. Just do the phlebotomy study.” But you know the phlebotomy study was an intrinsic part of you know this whole package.

I Right.

R And it made no sense on its own. So we said, well, we can’t... because it makes no sense... You’re going to... Unless we look at it in the context of this huge investigation, so called. You know we can’t do the phlebotomy, we can’t review it, we’ll, of course we’ll say no... because it makes no sense. ..

I Yeah, yeah...
R    Well that didn’t go over very well. One of the things I did at this point ... I was pretty much on my own again. [My coworker] was off elsewhere in the ... doing her thing. I took it upon myself to call up a lawyer ... one of the hospital lawyers
Participant #2

R    Okay, so, it was extremely difficult for [this hospital] to conceive of a situation where doing chart reviews, and patient and proxy interviews and trying to determine a mode of transmission or who infected who, contact follow up stuff, wasn’t research. From our end, it’s routine daily practice, and the methods don’t change a whole lot, depending whether the agent is known or unknown, or... so from our end, I suppose, things start to veer into research, if you’re using the occurrence of an outbreak to actually identify in the lab sense, a novel agent and characterize it.

I    Right.
R    Or you’re taking advantage of an outbreak to develop a new laboratory test or serology test or characterize that test against an existing gold standard. That piece of it is research, but the outbreak investigation and management is happening regardless whatever other research gets glommed on to it...

Later in the interview:
R    People have different takes on how it unfolded. If you ask the guy who [was at the community hospital] REB at the time... he is still almost apoplectic about how it unfolded. If you ask the public health people, they’ll say something along the lines of ... it was pretty straightforward... not, there were some research pieces that absolutely fell under the purview of the REB and those could have happened or not happened.
I    Right.
R    That was not, that was a separate issue from the investigation management of the outbreak and the HPPA is pretty clear about who has jurisdiction and authority, and what public health...
I    HPPA?
R    Health Protection and Promotion Act.
I    Okay, sorry.
R    ...can or cannot do and what they can or cannot have access to. But I think that goes to show emotions run very high in a crisis.

Participant #16

The interaction between public health and hospitals must be put in context. These institutions in Toronto have a separate governance structure, interact with each other only minimally and at least for community hospitals almost never collaborate with each other on research projects. Dr. Bonnie Henry, who was Associate Medical Officer of Health in Toronto in 2003, said at the Campbell commission:
“I think that the relationship between Public Health and health care facilities, hospitals, is a tricky issue and always has happened, particularly in Ontario, perhaps less so in places that have regionalized, where Public Health and facilities are all under the same structure administratively, organizationally, but in Ontario and Toronto, hospitals are publicly funded and privately run and they believe themselves to be private entities and I think they have evolved to the point, and certainly prior to the SARS outbreak, our relationship, Public Health’s relationship with health care facilities, was minimal and sometimes adversarial.”

This was reiterated by one of my respondents:

R after that, in practice it varies a lot, certainly at the time of the SARS outbreak, it varies a lot around the province. And also, I think with the capacity of the hospitals in more rural areas... there are no hospital epidemiologists. You might be lucky to have an infection control practitioner who’s ever had any specific training, and they’re much smaller communities all together.

I Right.

R So as a matter of course, public health would be in the hospital, working directly on outbreak investigation and management in that kind of context. In Toronto, there had been a much longer history of a kind of separation, certainly with the academic hospitals, very much which the academic hospitals, that internal nosocomial outbreaks, the hospital would handle, and anything in the community, public health handled.

I Okay, so...

R Technically that’s not the way the law goes. Technically, public health is accountable for outbreaks anywhere in that jurisdiction.

I Okay.

R but they sort of um, practice ...

I defined...

R Evolved. And you know certainly, in my experience academic hospitals in Toronto... Um, there’s some great infection control practitioners and infection control divisions and hospital epidemiologists, totally competent and capable. But the point I think, and it’s come up over and over in all kinds of reports is that, if you have that kind of divide in practice, it can end up like a fiefdom with no coordination, or much more limited coordination.

Participant #16

She makes the point here about the difference between small rural hospitals which have no epidemiologist on staff and so might be more familiar with public health investigations, and academic hospitals which are accustomed to doing their own outbreak investigation and where infectious disease specialists are perceived to be ‘totally competent and capable ’ to carry out outbreak investigations by public health officials. The community hospital falls into an area that
is between these two ends of the spectrum. It is a large urban community hospital that had a very small infection control department, which may not have had the depth of experience found in academic centres. This same participant later comments about this community hospital:

*It was one of the places that had and has for years, had really undervalued and under-resourced infection control... But I guess what I’m saying is there was very little culture there and other hospitals too, of handling outbreaks. So the whole thing was unfamiliar to them.*

Despite the submission of protocols to the REB at the community hospital and their subsequent withdrawal, public health officials felt that they were clear on what needed REB approval and what did not:

*I* Right... And how does it work in public health, like who decides what’s research and what’s outbreak investigation, how does that happen?
*R* Oh, outbreak investigation is not research. Outbreak investigation is bread and butter.
*I* No but there is a line...
*R* Not for us...
*I* Okay.
*R* Not for us... And I think that’s something that people outside public health, or certainly outside infection control, have a terrible time wrapping their head around.

Participant #16

Academic practitioners, however, were not so sure about the distinction.

*R* Oh Lord okay... why don’t I... It’s a little hard from my perspective, it remains a little difficult to separate out, research from outbreak investigation.
*I* well that’s important in itself...
*R* Yeah, that, that’s an important issue, so eh... I would label them the, the kind of main piece of data gathering and, and what we were doing at the beginning as outbreak investigation rather than research

Participant #6

*R* ... but the first... I was involved in SARS in a few odd capacities, like that weren’t; I wouldn’t say ... were not really research oriented. But because all of SARS was so new, sometimes it seems like research.

And later:
*R* I went with the team that went to the homes of nurses from Hospital X, who might or might not have been exposed to the illnesses since we went like door to door, doing nasopharyngeal swabs on them, but I think that was really an outbreak investigation
and not really research. It was looking for new information but from a public health point of view.

I Okay.

R as opposed to the research, the real... that’s just an example...

Participant #4

Academics treat a protocol as research when the same body of work performed by a public health official would be considered surveillance.

I yeah... right... And why is that research and not surveillance?

R Well, well, no... If public health were doing it for public health it would be surveillance. If I’m doing it for research purposes, it’s research.

I Okay...

R Unequivocally, okay...

I I’m still trying to grapple with the distinction... that...

R Well, ...in my view some of the things that we do, and their purpose in improving patient care ought to be being done as surveillance by public health., that doesn’t alter the fact that when a public health person is doing surveillance for the defined health of a population, that’s different from when, I have that data as an individual academic, even if it’s for the same purpose. Okay it’s ... you know our relationship with people is different ... I think... changing our attitudes towards clinical research ... and building clinical research... is what will make a difference to that because then there will be people who can do it, and hospitals will be ... used to doing it, ... people will expect it to happen.

Participant #6

Thus the distinction between what is research and what is surveillance or outbreak investigation became more than just an academic exercise. It mattered to people and there were downstream consequences of the allocation of a project to research. A project that is research is subject to scrutiny by the REB. Public health officers may feel that this scrutiny impedes their time sensitive interventions, thus creating tension between REBs and public health. Potential legal liability of staff working at the community hospital was utmost in one REB member’s mind as she spoke about one of the projects that was submitted and then retracted.

R See, one of the problems was that some of these protocols could be used to blame nurses and doctors at the hospital for the spread of SARS. That was a real concern that a couple of us had... especially these epidemiological ones. You know, how did SARS
get from the emerg to the ICU to this floor, to that floor, you know, who did what? Who screwed up here? That was the sense that we’re...

I Yeah
R We were getting. And we didn’t want that to that happen. We wanted to protect our people.

Participant #2

R The overriding concern with every one of these protocols was to protect the staff from possible eventual allegations of neglect or incompetence.
I hm hm
R And in addition also to protect them from any untoward emotional effects that the ... a lot of people were very upset and there was a widespread perception that perhaps more could be done to protect nurses and, especially from being infected. And, a large proportion of infections were among nurses, which was an unfortunate thing, but it’s the case so, I think, I think those were our main concerns.

Participant #15

Protection of staff members from liability while doing their job (if these procedures are regarded as routine outbreak investigation) does not fall to the REB. The distinction between what a staff member is asked to do for research and what is part of their regular job is something that was considered to be important by the REB at the academic centre, although liability was not raised by the academic personnel with whom I spoke. Participant #3 highlights the fact that this REB understands that staff members have individual rights, rights as staff members as well as rights as research participants if they choose to volunteer for a research project. She also notes how difficult this distinction is to make when hospital staff members are doing tasks that are not normally part of their job description as occurred during the SARS outbreak.

R but many of these psychological impact of SARS type studies were done on staff as well as patients... or, staff that became patients. And so another blur here was the ...which we work hard on usually to provide sort of extra rights to staff who become subjects in studies; because they have staff rights as well as individual rights. And they have staff rights under collective agreements and a variety of things like that.
I hm hm
R So in a typical staff study we try and distinguish what is part of their job and what they’re actually volunteering for and making sure that the results gathered in the research study don’t impact their daily work-life and work performance, and those sorts of things. And we get investigators and the institution to recognize those differences. So
are you asking someone to do this as part of their job, and therefore you don’t need our permission?

I Right.

R The research ethics permission to do this, or are you doing it as research, and they have rights as you know as subjects

I ...as research subjects...

R ...as research subjects and as staff...

I Right.

R So we usually spend a fair amount of time on those sorts of studies to try and make sure that everybody understands the distinction. In SARS, that was very blurred because staff were being asked to do things they would not otherwise do in a non-crisis situation.

Participant #3

17.213 Pressure by Investigators on REBs to Approve Protocols

As described in the previous chapter, many protocols were submitted to the two REBs. This influx of protocols, all of which were felt to be important by the investigators who submitted them, put pressure on the REBs to approve them quickly or the window of opportunity to generate new information might be lost. Some investigators applied extra pressure to get their protocols approved. This pressure became so intense at one point that REB staff feared for their jobs when the Assistant Deputy Minister became involved in the process as described below:

R See all of a sudden we started getting a number of different protocols coming in because we’re the epicenter, a lot of people; saw us as one giant cage of lab rats to...

I Yeah, right...

R ...to do whatever they wanted with... And, I think this is still the same one, I think this was the same study. The researcher called up one of the top people or the lead people in public health and told her that the hospital is not going to let us conduct this research, and then she called up the ADM, the Assistant Deputy Minister.

I Okay.

R And said, ‘guess what, the hospital’s ... those little pipsqueaks at the hospital are doing?’ The ADM called up the President of the hospital, and chewed him out. I believe the President was at a dinner or was somewhere. He was at some sort of meeting or something. And was called out to be chewed out by the ADM and then the President called the VP who was in charge of research and started yelling at her and then she called [an REB staff member] and I, and we had a little conference call, I remember this very clearly and she said what the hell are you guys doing? You can’t stop anything like this. We have to do this ... we have to do anything that they want ... basically we have to. We can’t get the Ministry mad at us. And it was not such a veiled threat that our
jobs were on the line. If we stood ... if we said no, kept saying no to these studies, we would be gone. And whereas I ... given my situation, I said well... screw that, you know, fire us...

I  Right.
R  Let me go to the papers with this one. You know. But [my coworker] was... who has a family, and [identifying material about the coworker].
I  She needed the income.
R  She needed the income.

Participant #2

Another REB member speculated that being on the hospital payroll as well as volunteering on the REB leaves one particularly vulnerable to this type of pressure. This highlights both the need for REBs to be at arm’s length from the institution, and the difficulty in doing so.

R  But you know, I suppose I’m in a privileged position because I’m not an employee of the hospital. And I can truly make independent decisions without fear of consequences that may affect my livelihood.
I  Hm hm
R  The worst that can happen ... tells me you’re no longer a member of the REB, I’ll say okay, goodbye, you know and I keep my practice, and you know this...
I  For sure...
R  ... I don’t expect the hospital would do that, okay. But if you are an employee on payroll, and you have ... of course the administration wants to get things moving, and you’re perceived as or you’re in a role where you are looked at... you might be perceived as slowing things down.
I  Hm hm
R  It’s very uncomfortable. Okay, and the other members of the REB who were on staff.
I  Yeah...
R  Are employed, I should say, employees of the hospital, on payroll.
I  Right.
R  They felt the pressure, you know, and they had to have a considerable, sort of moral strength to fight that. There’s a feeling that they should be abiding by their employers’ wishes.

Participant #15

The tension between the REB and Public Health and the pressure to approve protocols was not felt at the academic centre’s REB in the way that it was at the community hospital. One REB person at the academic centre speculated on this discrepancy:
we were unhampered in how we conducted the research ethics approval of any of the studies. I know this is not the same at every, or wasn’t the same with every institution. But we were left to deal with this independently as we always do, without any pressure to, apart from the usual kinds of pressures and the time pressure in this case, to approve things quickly for dealing with SARS. But we were unhampered by administration, public health, politics. We carried on business as usual. My suspicion was that either we were being allowed to carry on as usual or probably, more likely everybody else was so busy dealing with SARS that they didn’t even know we were carrying on...

R yeah right...

I Right, right.

R And I suspect the latter is more the case. So this is a different experience than for instance happened from the first hand testimonials at [the community hospital]. So we felt no pressure from the... those sorts of avenues that might have caused pressure in other areas.

I Right, right.

R Most of the studies that we saw were surveillance or infection pathology kinds of studies. So many of those studies that we saw were largely related to samples.

Participant #3

Perhaps the pressure to approve protocols was felt primarily at the community centre because it was an epicentre of disease. As such, public health officials were particularly interested in stopping whatever factors had allowed the illness to propagate from this centre. Many public health personnel were involved in these outbreak management activities, and all felt a great urgency to understand the transmission patterns and other environmental influences that facilitated it. Because there was confusion about what was research (and thus needing REB approval) and what was pure outbreak management as described above, and because of the urgency to curtail spread from this epicentre, public health investigators felt that they had to apply political pressure to get their protocols approved.

17.22 REBs Response to the Stressors

Very early on in my investigation, it was clear that usual REB processes were disrupted by the outbreak. I was aware of some of the responses of the REBs to the outbreak (e.g., the speed
with which the REBs were able to evaluate and approve the protocols that were submitted to them) from the ‘Two REBs’ study described in the previous chapter. The median number of days from submission to approval was 20 days (range 2 to 43 days) at the community hospital and 4 days (range -2 to 50 days) at the academic centre. (Table 16.1) It is important to note that protocols 3a and 22a were approved before they were officially submitted. In conversation with the researchers and the REBs, it was evident that much of the interaction had taken place on the phone ahead of the paper submission. Thus the REB knew that the submission was being formulated and what it entailed. Perhaps they had been submitted electronically, and paper copies not kept.

Both REBs changed the way they prioritized the review of submissions they received. At the community hospital, the REB thought they would remain closed until the outbreak was over. This was not workable once the time-sensitive SARS-related protocols began to arrive. This hospital only reviewed SARS-related protocols. There were too many other things going on in the hospital (e.g., quarantine of REB members, clinical staff becoming ill and requiring care, interaction with public health officials, enforcing the infection control measures especially at the hospital entrance etc.) to do anything else given the small size of the department and the fact that REB staff and REB members were seconded to other jobs and not available for routine REB meetings. This REB does not use expedited review very frequently and the format that was devised for their ‘crisis review’ of SARS-related protocols was not an expedited type of review. The ‘crisis review’ panel consisted of the five people required by the TCPS. They sometimes met face-to-face, although they wore full protective gear (masks, gowns, goggles etc.), and the community member attended by phone. In order for a research protocol to be approved, all members of the REB had to be in agreement. After the outbreak was over, this format was
formally written up as a standard operating procedure (SOP) for use during a crisis, and was accepted by the governing board of the hospital. At the academic centre, SARS-related protocols were also given priority. However, they were also able to hold some regularly scheduled REB meetings to review protocols that had been submitted prior to and during the outbreak. These meetings involved the usual REB members, used the regular format, but occurred by teleconference. The procedure that was used to review the SARS-related protocols was less complex than that used at the community hospital. Most of the protocols received at this centre were deemed to be below the level of minimal risk and thus received expedited review as described above. Those protocols that were more risky were reviewed by a combination of usual REB members and consultants that were recruited to provide specialized expertise.

17.23 Researchers’ Response to the Outbreak

Researchers realized that there were many questions that needed to be answered and began to develop SARS-related research protocols as soon as it became apparent that an outbreak was in progress. These protocols were written very quickly and their quality varied.

R ... and that was kind of like when everything started snowballing, cause then we knew what the methodology was and it was a matter of writing the protocol and writing the piece. And that took me probably Friday night to Monday morning.
I Wow that was fast.
R But then, that was not(?) writing the protocol, that was the conceptualization of it and to bring it together, but then the how do we do this became the next piece...
Participant #9

R But there were a couple we said no to, and there was one in particular that was a, I think it was an epidemiology study ... sponsored by Public Health that in a very complicated - oh this one had about five parts to it. And they kept adding parts. It was a really complicated protocol and frankly not well thought out.
I So I think that’s part of the problem.
Yeah ... they were just writing this ... don’t get me wrong. I’m not condemning these people or really I’m not even criticizing them. Here they were fighting this unknown bug...

I  

R  For sixteen hours of a day, going home getting sleep for two hours, and then starting to write a protocol, for the next six hours.

I  Yeah, it’s not the best conditions.

R  No, it wasn’t. And we got a number of studies presented by people who have presented studies to us before that were just exceptional. Well written, well researched, well justified. So, getting this stuff, that was not well researched, not well written and not justified at all, was surprising and inconsistent.

I  So...and were these... were they... the not so great protocols, were they from people who were used to putting protocols together?

R  Yeah, oh yeah...

I  so these were experienced people...

R  These were very experienced people...

Participant #2

This speed with which they were written has implications for REBs as does the fact that most of the protocols were not externally funded. As mentioned previously, lack of external funding means that the proposals have not been peer reviewed and so have not received the scientific scrutiny that occurs as part of the usual peer review process.

Several protocols put special mechanisms in place to recruit potential participants and to obtain informed consent.

I  yeah... right... Let’s see... So were there any other special issues that came up as you reviewed the protocols? That you can remember?

R  Well, I think the recruitment process was a very special issue, because the study coordinator wouldn’t necessarily want to put themselves at risk or the investigator to approach the patient face to face, and the consenting process would have been a little bit trickier, a lot of it would have had to be over the phone, or... not standard way of face to face discussion and, take the consent home, discuss it with your family and doctor, cause a lot of times there wasn’t time for that, so... the consenting process and the recruitment was a concern, and we did have to ask additional questions around that.

I  Ask questions of the investigators...?

R  Yeah, its how are you going to approach this, or if the patients were quite ill... the competency level.

I  Yeah...

R  Like a lot of that...

I  so these were discussions you had with the investigators...?
R  Right... It’s part of the questions in the application, just more information may have been required than we generally need.

Participant # 11

In the protocol discussed by participant #9 below, a phone and internet consent process was used instead of the usual face-to-face process. In this case, the REB made sure that it was impossible for researchers to trace the responses back to a person or to a computer. This occurred in several protocols with the information technology (IT) department helping to make this possible.

R  it was how are we going to do the data gathering? So we had a group around here, and some of the informatics people, we designed a website, so that they could sign on to a website wherever they were, and go through the whole consent process, and respond to the interview question online. And then we also, I phoned the telecom people and said, I want to do this on a telephone. And so the people could call in, ... press one for whatever participant group they were, press two to listen to the consent, press three to agree to the consent, or exit, and then they were asked a question online, and they got to respond to it on a voice mail. And then it came to us, and we had someone transcribe it. So it was very fascinating, how we made the data gathering piece to fit the fact that we couldn’t go...

I  Right, right.

R  And then the whole recruitment piece was a challenge and ... So all along the way, it was like, how are we going to do this without actually being able to be there. So we started giving out flyers as people came in the doors in the morning. We had flyers put on all the meal trays that went into the patient rooms. And it was fascinating. But I think the most phenomenal part of it was, if I had tried to do that study today, it would have taken me six months to make it happen. This took, six or eight days. Right, because people just, it was like, it was just, everything that was going on, it was all part of everybody’s step to the plate and respond to this crisis. And we’re just going to make this happen. So right from, it probably would have taken me three weeks or a month to even get in contact with the proper person in the telecommunications that would say yes we can make you a phone line, and we can set up these mail boxes in this way, with these press buttons. And it kind of happened. Right... In a few days when we kind of... Once we had an idea of how we’re going to do it, then it was a matter of writing the consents and writing the protocol to match how we were going to do the data gathering so we could get ethics approval.

Participant #9

Researchers also had to change the way that they interacted with each other and how they acquired their data.
And you know, it was just fraught with challenges because if I went to let’s say hospital X, I couldn’t come back to my office at hospital Y. Then I’d have to work from my home office, until...

you couldn’t go back that day.

No, I’d have to be off for ten days, and then I’d have to work from my home office, because I was on quarantine. They wouldn’t allow me to go back in. So I was meeting my nurses in the parking lot. So that I wasn’t in their facility and I could say with a clear conscience that no I was not in their hospital.

you could not enter the...

...another facility.... Yes, so it was very interesting.

This occurred even when the study was a retrospective chart review as participant #8 discusses below:

And he was very clear, he said, you know, we [the research team] will never meet face to face. The team will never meet face to face because we can’t have this happen again. [quarantine of all team members] And so we had daily conference calls.

Later in the interview

And the charts started to flow to my house.

Oh so somebody... what... did they photocopy everything?

Yeah, because we couldn’t go, because of all the quarantine, infectious disease issues, the study team couldn’t go from hospital to hospital.

Later in the interview

So we um, so yeah we couldn’t go into the study hospitals, and the team never met face to face. The only people..

So even your two medical students ??

They basically moved into my house, for about a month. And so, we had to figure this out. So what we did was, we had all the charts photocopied, at the hospitals, the medical records did this very, very quickly. I think within a week or two.

Later in the interview

And then, the chief of staff or someone, or the ID doctor would say, yes. And then they would say, medical records here’s the list of the 8 patients in the hospital, they have SARS. Photocopy these charts. Send them..

.. send them off.

.. to [the researcher’s] apartment in [region of the city]. And so, so we’re getting these photocopied boxes, started arriving by taxi cab mostly. And so I’ll never forget, because when we, , this was before we knew you know how virulent things were, and how long the virus lasted. So we even were thinking you know..these are real charts that are going on the photocopy machine, and people are touching them and touching the clean papers, there’s SARS virus on these photocopies.

Yes.
R So my crude kind of infection control measure was to leave the charts in our front porch outside for 24 hours... before bringing them in. I just did that, cause it seemed to make sense.

I Yeah.

R And I would also, I think the first week, or first days, first few days, I we were actually wearing gloves and masks, and we were dealing with these photocopies. So I'll never forget this one, this one taxi driver, driving down my driveway... and walking up with a big box, that said, “SARS Confidential Research, [names the doctor].” And I went to the door with gloves and mask. He just lost it, he freaked.. because he was so scared. You know there’s probably a live virus in there. You know. So you can tell it’s quite an experience.

Participant #8

I suspect that this level of detail, i.e., that the data extraction, entering and cleaning were taking place in the researcher’s home was not known to the REB. It was not in the files of this protocol which I reviewed, although someone at each hospital knew this since photocopies were sent to the correct location. Confidentiality is one of the guiding ethical principles of the TCPS, and REBs usually want to be aware of and approve the procedures that investigators are using to ensure confidentiality of patient data. If REBs had been equipped to monitor ongoing studies during the SARS outbreak, non-standard practices which might have an impact on confidentiality might have been acknowledged and approved or modified as required.

When initially thinking about my data, I was struck by the fact that everyone talked about change. The REBs had changed their procedures, their priorities and sped up the review process for SARS-related projects. Researchers changed how quickly they wrote their protocols, how they obtained consent from their participants and how they interacted with the REBs. Public health personnel changed their interaction with hospitals and began playing a more active role in infection control and outbreak investigation in community hospitals. They had little choice in making these changes, since to do nothing in this dire time, was not morally acceptable. In a brainstorming session with colleagues, someone came up with ‘forced to adapt’ as the central
theme of my analysis. It seemed to fit. However, on further reflection and on rereading some of
the quotes from my interviewees, I began to see the deeper issues and the implication of what my
participants were saying. When speaking about the pressure that was applied to the community
hospital REB, they were really discussing the lack of arm’s length between the REB and the
institution. Broader issues about policy were being raised, including institutional conflict of
interest (COI). These issues are explored in greater detail in the discussion section of this chapter.

17.24 Interaction between the ‘Three Solitudes’

Researchers, public health officials and REBs were forced to interact with each other and
the interaction was not always collegial as described above by an REB member. One public health
official commented that researchers and public health personnel got in each other’s way and
sometimes obstructed the work of the other. One researcher described to me how she manipulated
REBs into approving her protocol. Public health seemed not to know if some of their protocols
were research and at least one of their proposals was submitted to the REB and later retracted.
There was coercion and political pressure applied to at least one of the REBs that I studied.
Details of these interactions are explored in more detail below.
Several researchers commented to me that they were very satisfied with the research ethics review process when a single site was involved.

R ... our REB ... it went very quickly, very effectively, and I think that quickness was also in recognition of the fact that it was dealing with SARS and it was such a time sensitive project. And they pumped it through very quickly. I would say that our interactions with the REB for that study were outstanding... um there was a recognition that it was important and had to be done quickly.

Participant #10

I When it came to getting REB approval..
R Hm hm..
I Um... what was your experience there?
R I was surprised how really easy it was; we asked for an expedited approval and we did the forms... and it was really very easy. We submitted them, and I can’t remember exactly what the time frame was that it came back in, but it was very timely, there weren’t any questions.. it was approved. It wasn’t a study that... I mean, there was obviously some danger and some risk of upsetting people. But I don’t think it was one of those studies that was sort of high risk - or invasive in any way. And so we were very pleased; we
thought maybe there might be something about the questions. But there was nothing. It just came back approved, and... we were quite pleased.

Participant #7

However, the single center studies were primarily conducted from the academic centre. There were only two protocols at the community hospital that were single centre studies: they were both submitted after new cases were no longer occurring, and they were approved in August and September 2003 i.e., after the infection control restrictions were lifted (approval time of 23 and 46 days). I did not speak with either of these investigators about this aspect of their work. Thus it is possible that the satisfaction expressed by researchers was only felt at the academic centre, particularly as researchers mentioned that community hospitals responded more slowly for the multi-site proposals:

I Okay, yeah... And why do you think the community hospitals were so slow?

R I think they didn’t have a lot of experience generally, the REBs weren’t as sophisticated, number one. I don’t think the people who were on the REB were as good as in tertiary care settings ... lack of sophistication. And maybe they didn’t quite understand that this was very time dependent, that we really needed, ... as much as we, tried to push it, they went at their own pace, and that was it.

I Yeah, yeah... So was your interaction with them different than usual. Like usually you just, submit the protocol and sort of wait to hear...

R Well I think all interactions at that point were unusual because this was during the SARS outbreak, right.

Participant #17

This same participant speculated about other reasons that may have hindered the review process at one community hospital.

R Okay. And there was varying levels of expertise, among the committees, obviously the tertiary care hospitals were able to, the university affiliated hospitals were able to ..., I think we got granted expedited review and were able to competently handle it. The problem came with some of the community hospitals and I won’t mention any names but there were some community hospitals that felt I, you know they never said that directly but between the lines, were actually putting up barriers to this. They didn’t like the fact that they had had SARS in their hospital and I think they realized legally, they might be facing a challenge specifically from nurses, who felt you know had gotten SARS, and felt they weren’t being adequately protected. And my feeling was that some of these, at least one of
these, these places was using that as an excuse, not to go forward with the research. Not to try to understand what made nurses sick. That was specifically geared towards the project that we were working on.

I Yeah... Um...

R Which I thought was totally, I couldn’t believe it... you know to me this was, I felt this was a corruption... of the REB process. In other words, it was not dealing with ethical issues; it was using it as a front, to deal with medical/legal issues... to medical/legal risk.

I and was that feeling coming from the REB?

R No, that was from me, yes, it was directly coming from the chair of the REB... the message of stalling and we’re not sure about this, and quibbling about points.

I hm hm

R Okay, this was my interpretation.

I and you felt that it wasn’t directly related to the protocol at hand?

R Correct... I felt that there was something behind this, that this was in a...

I Right.

R ... and I felt that there was likely some legal concerns...

I But nobody ever said that to you?

R Um... this is what I’m trying to think, I think it was insinuated by one of the co-investigators ... a clinician at one of these hospitals.

I at one of the sites, yeah...

R Yeah, that this was probably the underlying reason.

Participant #17

Another participant saw the conflict as something different. She felt that the root of the conflict was a disagreement about what was public health outbreak management and what was research that required individual consents even for chart reviews.

[the community hospital] ... dealing with the [a community hospital] was, a level at which there was substantial amount of disagreement, about what was outbreak investigation, and what was research. And, from my perspective and perspectives are different, the [community hospital] defined as research something that I saw as critical to patient care in the outbreak. They felt that what I thought were critical elements of data collection for the purposes of protecting patients in as it turned out, phase 2 of the outbreak - no one knew that phase 2 of the outbreak was going to happen, okay...but critical issues of data that needed to be collected on a short time-line... so that you could define how patients need to be protected were seen by their ethics department ... I don’t know what else was going on in the hospital, as research, and as research stuff that could not be done without a considerably longer review and consent, express consent from patients - no chart reviews without consent from patients. And I respectfully disagree with the position of the [a community hospital] on that. And there was a certain amount of argument in that about, I think about kind of control, there was some control issues about what was [a community hospital]’s and, and what was not [a community hospital]’s, but I think a lot of
it was an honest disagreement about what some people saw as research and what other people saw as population-patient care.

Participant #6

Particularly at the academic center, researchers felt that the REB was doing what it could to facilitate research efforts. Much of this facilitation took the form of phone conversations, as opposed to the usual more formal paper based interactions.

R ... well there was one person in one group that made it non-issue. [This person] has a very clear sense of what needs to be done and when you have to bend the rules, and how you do things and he facilitated an enormous number of things, within the downtown teaching hospitals. So the ethics issues we had were, first of all, that there are just some things you have to do, so the ethical issues that I had to deal with,

I Right...

R the stuff that I had to deal with was just a bunch of necessary paper work and stuff... that is really hard to do and get your head around, and get organized. And it had to be done for every hospital, in the system.

Participant #6

R ... I talked to the chair, and I said, this is what I want to do and ... if I send it over can you review it, like in the next couple of days. And they did!

I Wow.

R That never happens now. Right...

later in the interview

I So and then, for REB approval you said you phoned the chair?

R Yeah...

I and, is that what you normally do phone up the person

R No...Oh God no... It goes through a process. Right, and it goes over to their ...

I Yeah...

R ... and, we, no he just...he’s got all kinds of people that make that make things happen.

I Yeah...

R And my co-investigator on it...

I Hm hm

R ... we just sat here and we thought well how are we going to get ethics approval...we can’t... we don’t want to wait for however long, so we phoned up [the chair of the REB], and we said, look we’re doing this... and if we could have it to you by tomorrow, what do you think? And he said, well send it to me and I’ll review it. So he too dropped what he was doing and reviewed stuff. And I’m guessing he did that for other studies too because there were some things that happened, and it just, so he probably did it with a small... and it wasn’t like it was a study that was an intervention study, where they needed to have a full board review, it would have qualified for expedited anyway...

I Okay. Yeah.

R Because it wasn’t like we were doing intervention on people.
Participant #9

R  ... our REB ... it went very quickly, very effectively, and I think that quickness was also in recognition of the fact that it was dealing with SARS and it was such a time sensitive project. And they pumped it through very quickly. I would say that our interactions with the REB for that study were outstanding... um there was a recognition that it was important and had to be done quickly.

Participant #10

REB members agreed that much more communication occurred over the phone than was usual. This allowed for a greater understanding of the protocols on the part of the REB, and at least in one case, a discussion about procedures that might be used to protect the anonymity of respondents to a telephone and on-line survey. These conversations allowed a quicker turn-around time from submission to approval. While some phone communication does occur in normal times, researchers commented that this occurred more frequently during the submission process of their SARS protocols. At least at the academic center, REB members saw their role as facilitators to get the process completed as quickly, but as thoroughly as possible. This facilitation was recognized and appreciated by several researchers that I spoke with.

R  So the SARS protocols that I received, I usually received a phone call to say it was coming.
I  Okay.
R  Umm...
I  Is that normal?
R  No... Generally they ask where the chair is, and would he be available because of the necessities of put it through quickly and a lot of the investigators asked about the process, did they have to wait for the next full board meeting to have the protocol reviewed.
I  so there was a lot more phone communication than usual.
R  Yes. Yes. And ... as we knew it was an emergency, and we had to treat them as emergency protocols ... because there was a short time frame that they had to, study the ... patients that were affected with it.
I  Right.
R  So we did our best to facilitate that... in different ways... and I was the facilitator...
Satisfaction with the research ethics review process was not felt when studies were carried out at more than one site, and the studies were submitted to several or many REBs. Researchers felt that this was a waste of their time, particularly when there was an urgent need for the potential knowledge to be acquired from the studies.

R ... that added to the stress of trying, ... as well as the timeline where there is a feeling that we had to move quickly to do this study. So I was involved in all of the filling out and delivering the ethics forms... again it’s not something that I think is really crystal clear in my memory, except for that, it seemed to take ... a lot of ... it was very time consuming. We had to get forms from a large number of hospitals, which was always changing and increasing. And, basically by the time that the ethics approval would come in from certain hospitals, it was other hospitals had been designated as the hospitals that were going to care for SARS patients.

I so sometimes you were applying to the wrong places.

R Yeah, they weren’t, they weren’t the wrong... I, and, and everything(?) with the wrong place but certainly from my point of view at the time I didn’t understand why you couldn’t apply to the central source and say we want ethics approval at every hospital to do this...

I Right.

R Uh, we also had to apply nationally, because of the experimental nature of [the trial].

I Right...

R ... so we also applied nationally and...

I nationally... you mean, Health Canada?

R Health Canada yeah...

Participant #4

I Right, right. I guess the fact that we organized our clinic so that we only had to submit to one REB. The logistical REB things at all the other hospitals is a nightmare.

I Yeah... for sure...

R And so... that again speaks to the centralized process, right, for patient identification but also centralization for REB approval for projects that are going to involve - right, people all across a city or a province or whatever ... cause what you’ve got REB approval at about 21 hospitals or something? And was it 21?

I I think so yeah, 21 or 22.

R Something like that. Yeah, I mean some ridiculous number and I think that the time and effort on your part, the hospital REB committees part. All this wasted time. I mean they needed to ... that process needed to happen but there’s a more efficient way to get to that... or a more efficient way to deal with that process.

I Yeah...

R And I think that the inefficiency of that was also just glaring.

Participant #1
R I think that, you know again, as I said, working through the details of how you would get ultra-expedited review of protocols in a safe manner.

I Hm hm

R Cause you don’t want to go the other route, which is do whatever the hell you want, we’re in an emergency.

I Yeah...

R Like you’ve got to have a balance there. And the only way you can have that balance is thinking about it ahead of time. Also having that review stick for multiple hospitals. ... rather than doing the ... you have applied, here, here, here. I mean that already drives me nuts... Now... Okay.

I Yeah...

R Having to apply to six different REBs if you’re doing anything outside of the hospital. It becomes really ridiculous.

I So it... Do you think that’s feasible to get some kind of um, a board that would be answer, or that would, that hospitals would agree to submit their, their protocols to and, be happy with the legalities of it..

R I honestly think, it is, it is an obscene waste of resources. That we constantly duplicate later in the interview:

R But again I would like to think that you could organize that, such that, if you had a multi-centre study, you wouldn’t have to apply multiple times, you know. You apply to U of T. You apply to [her own hospital]. If I want to do stuff at [another academic hospital], I have to apply [the other academic hospital], even though it’s the same chair of the REB. It becomes this ... how much time do you think I have? Cause it takes hours... to reformat these things. And, it may not be so bad for the big established researchers that have huge research teams; that have a person who’s doing that for them. I don’t have anybody, I do it myself.

Participant #13

As several of these participants mentioned, researchers felt that some sort of centralized process would have been helpful. Several of them mentioned that this process would need to be set up ahead of time, and that should another outbreak occur now, we would be no further ahead in this area.

R So, if there ever was a pandemic, based on what I saw, the way to set it up, in it... there are way better ways to set it up in advance. Number one: to get everybody to allow deferral to a central REB.

I Yeah...

R And to get everybody to decide in advance, that copying with names is going to be okay. To get every CEO, to sign on, that no doctor is going to be allowed to block this for political reasons. Like those are things you can prepare for. But those things which were difficult but doable, but probably took about seven days, could be done in one day, if you thought about it in advance.
Right, if everybody was on board. Although with the CEO’s changing, you’d have to...

You’d put it in to hospital, by... I mean there’s... if we’re trying to institutionalize things for a pandemic, these are things that you think about in advance, you set them up in advance.

Yeah...

You have a deferral mechanism, you flip a switch, you say, now defer to the pandemic office, and these are the rules by which they operate and they over... basically supersedes everything in your hospital.

Yes...

It’s completely doable.

Participant #12

One senior researcher described her interactions with REBs and what she did to get her protocol approved at the eleven sites to which it was submitted. She maintains that this is the only way to get approvals in the timelines that were required. She sought allies within the hierarchy of the hospital, and got them to apply pressure to the REB. Even once the REB had approved the study, she talks of having to convince the staff in medical records to set aside procedures that are normally followed to protect the confidentiality of patients’ records.

The REBs were on side very quickly to turn it around.

and how did that work. Did you call them?

It was me on the phone; you know what I’m like.

Yeah...

You know when I’m not taking no for an answer.

Right.

You know when I’ve got them by the balls, and I’m just pulling. Like I just would not take no for an answer...

so did you do formal submissions?

Oh yeah... Oh, no, no... we, we did all of that.

Yeah...

But I clearly said to them, “You need to do this quickly. You need to Xerox the charts, you need to get them to agree to send them, and the hard part for you is going to be do them with the patient names on them.

Yeah...

For the most part, they all said yes, because it was an international emergency. The only, you know some of it, required some explanation.

Right.

But it, and then it was worse than that because it wasn’t just that the administration said yes, and the REB said yes, the medical records people had to do it.

Yes...
Like those are the people that actually had to do it. So that again it’s four years ago, my recollection is, that that took some doing in some places. Like I personally had to phone the head of medical records and do what I had to do, be nice or threatening.

... whatever was going to work. And I can be both. As you know... There were only two, you know, everybody needed some explanation which is normal.

Some places needed no explanation. There were only two places that I can recall where I had trouble. One... now... the question is... how much I should tell you.

It’s completely up to you. I will do absolutely my best to keep it confidential and not... reveal names. But... you know..

Okay... so, there was one hospital where there were a large number of cases.

Right.

Where the administration did not want to do this because they had legal concerns. Not just about the privacy, but about revealing what had happened there. You can guess what hospital that was.

Yeah...

The chair of their MAC [Medical Advisory Committee] was totally instrumental in helping me convince their administration. This man was a [named his specialty] and he... was very motivated to do this study. And without him, I’m not sure I would have been able to convince them. No, so I had to enlist an ally.

Right.

And, I said to them, look. You’re the people that caused this. How’s it going to look, if you’re the only hospital that isn’t part of the study? How can you possibly refuse?

Yeah...

They quickly, the lawyer quickly bought that. So you know, it’s just using common sense... it’s half bullying ... but you know what... it would... forget about my political skills, which I think were very considerable, in this venture, it was the right thing to do. And that’s the reason I won it.

This researcher was manipulating the REBs and anyone else in the institution who might block her study. She used bullying and political skills and the protocol went forward. According to this researcher ‘it was the right thing to do’. Thus interactions between researchers and REB members became more difficult when many REBs had to be dealt with. A system of multi-centre review that was familiar to both researchers and REB members might have alleviated some of this manipulation since the approval decisions would have been one step removed from the participating institutions.
One public health official discussed what it was like to work in an environment where academic research was carried out. She felt that their *modus operandi* impeded her ability to carry out her outbreak investigation. She also felt that the way that the CIHR funding was allocated was not advantageous to the public health outbreak containment. There was also the feeling that local front line clinicians who were also researchers were disadvantaged by the funding requirements since they had not had the time to develop a research protocol.

R The one that I was more directly involved with, that... and it, that became an issue, because once those charts were taken by that research group, they would not share any of that information on an ongoing basis with the Outbreak Response Team.

I Oh, why not?

R Because they said it was research and so they aren’t allowed to share their research findings... with...

I Oh the research findings ... I thought you meant they couldn’t share the charts.

R Well they wouldn’t share any of it. And they actually physically took the charts and refused to share information.

I Yeah, I can see that would be problematic.

R So that was a huge issue. Particularly because a number of the patients whose charts they had, had died and we were doing reviews to try and determine, whether ... there was trace back going on to try and determine who was in what category and who might have been in contact with them and stuff, so those charts became unavailable to the outbreak investigation team.

I hm hm

R This research project started.

I Yeah, that doesn’t sound like a good thing.

R No, it wasn’t. And that created a lot of angst, and tension, between the provincial level people who funded this research and the researchers who said it’s ours and we can’t share it with anybody.

I Hm hm ... yeah...

R And you know that’s clearly my point of view...

I Right eh heh...

R I thought. And there were a number of individual situations where ... that hampered our ability to link certain cases.
She felt that the public health effort to contain the outbreak was obstructed by the presence of the researchers who claimed ownership of the patient data and that this created angst and tension in a working environment that was already very stressful.

*Later in the interview*

R The one thing, just going back to the...
I Oh absolutely...
R ... SARS outbreak, there was one thing that was really, really, really upsetting... and really screws up a whole bunch of things.
I Yeah.
R Was when CIHR announced that they were doing a special grant thing...
I Yeah.
R to fund research into SARS...
I Hm hm
R ... right in the middle of the outbreak..
I Yeah...
R That became such a difficult ... it really screwed up our ability to do routine public health investigation. And, it alienated a number of people who were very closely working with us during that outbreak. For example, most of the researchers in Toronto, and most of the clinical researchers in Toronto were intimately involved with the outbreak response, and didn’t have time to put together a CIHR grant proposal.
I Right.
R Surprise, surprise...
I Yeah, right...
R You know, ... four grants were awarded, all of them were with principal investigators that were outside the city of Toronto. That was a slap in the face to all of the people who were working so hard trying to control this ...
I Right.
R And that was to me it was unethical, and it was just it was terrible.
I Yeah.
R Terrible.
I and it was because the Toronto people didn’t have time.
R Oh we didn’t have time, and, it also meant that there as now this group of researchers from all across the country who were just clamoring and, ... beating down our door to get data that they thought they were entitled to, because they got these grants.
I Yeah.
R It really... put a spanner in the works... I can’t overestimate.
I What...
R ... how detrimental that was on our ability to do anything...
I so what should have they done?
R They should have well, they could have done a couple of things. One, why do it right in the middle of the outbreak. Sure there were some key, clinical questions that needed to be answered. Why not support the people who were doing the investigations, things went
on, for example there was ongoing looking at, [names one investigator] for example was... looking at different regimens of steroid use.

I  hm hm
R  To see if it had any benefit.
I  Yeah.
R  And she didn’t get funded cause she didn’t have time to apply for a CIHR grant. Why not put the money into what was going on on the ground at the time, rather than coming up with a separate...
I  We’re so in to our system of you have to...
R  Aghh...
I  ... write up something and get it approved and, ??
R  ... and then all of the clinicians, many of clinicians, not all of them, a number of people who were working with us, in the various hospitals, and at the provincial operation centre and whatever ... everybody became very suspicious of each other. In fact well, are you doing that for a grant, or are you doing that because we need it for this or that... and so, it really created a lot of tension amongst people, unnecessarily.
I  Hm, yeah, that’s really interesting...
R  And facilities were very reluctant to share any information because they didn’t know if people were using it for ... for what purpose. And, rightly so, I mean it created a lot of mistrust... And it also created a huge burden on for example Toronto Public Health; because two ... well actually three of the four grants that were funded assumed that I would give them access to the patient files that we had at Toronto Public Health.
I  Right.
R  And that... I said no way that I could not give them names and contact information of people who were felt had SARS, without asking their permission.
I  Right.
R  And I had no time to do that now, and I wasn’t able to do that ‘til considerably afterwards.
I  Okay.
R  And you know, these were people who went through a terribly, terribly traumatic time, and the last thing they needed was four or five different people calling them to ask them if they want to participate in a study.
I  Yeah...
R  So we said... no, we will not give any contact information and, personally I felt like that wasn’t, that we were not able to do that. After things had settled down we sent them a letter... and said there’s a number of research studies going on, are you interested in participating, would you allow your samples or charts to be reviewed but...
I  hm hm
R  ... not talk to somebody... and you know there’s different options. And we ...
I  Right.
R  ... sent those letters and then followed up with everybody with a phone call.
I  Okay. And what kind of response did you get to that?
R  You know, ... probably a third of people said, yes, I’ll, I’ll??
I  only a third...
It is interesting to me how few people were willing to speak with researchers after they had first been approached by a public health official. Having SARS, and/or having a relative with SARS was very traumatic and this public health official reports that a high proportion of patients did not want to talk about it at all to researchers.

**17.243 Public Health/REB Interaction**

The public health units in Toronto during the SARS outbreak did not have REBs affiliated with them. There was also a lack of resources to conduct research within the public health system although research was part of the mandate of public health officers:

```
I  Yeah, yeah... so part of your mandate should be to...
R  Yeah, part of my responsibility and part of the expectations of my bosses is that I do research and publish it.
I  And yet there's no infrastructure.
R  hm hm
I  ... and no money, and no...
R  No it's very difficult.
I  Yeah...
R  Very difficult... But then we struggle....
Participant #19
```

This lack of resources and availability of a local REB familiar with public health protocols and the fuzzy boundary between public health practice and public health research point to a lack of familiarity on the part of public health officials with REBs and on the part of REBs about public health research and a lack of interaction between the two groups. In fact, the academic institution did not interact
with the public health office at all. The protocols that were submitted to the community hospital REB and then retracted reinforce this notion. The coercion discussed above by participant #2 involved a public health protocol. Thus the interaction of the public health office with the community hospital REB was fraught with tension and difficulty, and at times coercion to approve protocols occurred.

17.3 Discussion about the Three Solitudes Study

In this chapter I have presented a grounded theory of the impact of the SARS outbreak on the research ethics review system in Toronto as it processed SARS-related protocols submitted for REB review. In this theory, I have tried to capture the ideas presented to me by my interviewees, elaborate the interrelationships between them and provide explanatory power to understand the intricacies of the stressors felt by REBs and the responses to them by REBs, researchers and public health during the SARS outbreak. As a result of this study, I have learned that when REBs, researchers and public health are not effectively communicating with each other during a public emergency, the work of each group is disrupted. Each of the solitudes (REBs, researchers and public health) works largely in isolation under normal circumstances and this strategy does not work well during a public emergency. The distinction between public health research and outbreak management continues to be unclear and this caused problems both for the REB and public health officials. I also learned that the governance structure of research ethics review in Canada, in particular the reporting structure of REBs to their institutions allows for conflict of interest (COI) to be felt and to be disruptive to REBs. There was also a need for some form of multi-centre review for quick and thorough review of protocols to be carried out at multiple sites.

In the schematic of my theory, I have depicted REBs, researchers and public health far from each other and each is enclosed in its own box. According to my interviewees, that is how they
normally function. The system may work well under usual circumstances, but when subjected to the type of pressure that was felt during the SARS outbreak, weaknesses become apparent. Public health surveillance and outbreak containment is enormously complicated when it is done on the scale that was required during the SARS outbreak in Toronto. The lack of co-operation between some REBs and public health is distressing. Some researchers put pressure on REBs and tried to manipulate their decisions, although the interaction was more one of negotiation rather than confrontation and the pressure by researchers was not carried to the level that public health officers were able to exert. Each of these groups i.e., research ethics boards, public health officials and researchers is accustomed to working within its own silo – they formed three solitudes – a particularly Canadian metaphor.

The guidelines, legislation and the literature about REBs have been developed primarily with the goal to protect the research subject based on the principle of autonomy. Public health on the other hand is based on the good of the community and population health and is mandated by legislation. The role of the Public Health Agency of Canada (PHAC) as stated on their web site is to:

“1) Promote health;
2) Prevent and control chronic diseases and injuries;
3) Prevent and control infectious diseases;
4) Prepare for and respond to public health emergencies, and
5) Strengthen public health capacity in a manner consistent with a shared understanding of the determinants of health and of the common factors that maintain health or lead to disease and injury.”

Wallack and Lawrence comment that the first language of North American culture is individualism, and the second language is one of community that is “rooted in egalitarianism, humanitarianism, and human interconnection”. It is this second language that is used by public health who are interested in the health of the community. Clinical researchers, on the other hand, are very much focused on individuals, individual care and research about what will improve an individual’s health. Given this difference in focus and in language, it is perhaps not surprising that public health practitioners have
difficulty communicating the importance of their work to the general medical community and that clinicians fail to understand the strategies and methods that they use. While hospital-based REBs do think about harms and benefits to the community, they are primarily focused on the risks and benefits of the research project to an individual. Perhaps, particularly during a public emergency, researchers and REBs need to think more in terms of community benefits and risks of the protocols that they propose and review.

Participant #3 comments that the political pressure was not felt at the academic centre, and that research was not on the radar of the command centre of this institution’s response to the outbreak. While this is true, the question remains why it was not on their radar and why the command centre was not asked to pressure the REB about any of the protocols submitted. One explanation may be that research ethics boards, public health officials and researchers are closer at academic centres and that some bridges exist between them. Research is a mandate of this hospital and researchers and REBs, while their interactions are not without frustration at times, are familiar with each other, with the other’s challenges and with the other’s language. The links between public health and the academic centre, while not as strong as those between researchers and REB, are there. For instance, one of the senior consultants to the Toronto public health unit has a cross-appointment to the academic centre that I studied. She is well respected and carries out much research that is very similar to some public health projects and surveillance. She suggests that an increased emphasis and funding for research in public health units would help to bridge the gap between hospital-based researchers and public health research. I think that even had this hospital been an epicentre of disease spread, because of the links mentioned above and the resulting familiarity with the work of the other, the interactions between the solitudes of research ethics boards, public health officials and researchers would have been less confrontational.
The debate about what is public health surveillance and what is public health research continues. Bayer and Fairchild in their article in Science in 2004 have provided a summary of the evolution of thought about this from the US perspective. To date, there has been no clarification about this distinction from any Canadian sources, although the Public Health Agency of Canada (PHAC) is struggling with this issue as are some local public health units. I can now provide the perspective of academics and public health professionals who worked during the SARS outbreak in Toronto to curtail the spread of the virus. Confusion about what required REB approval and what did not was present in the Canadian environment as evidenced by my interviewees. As discussed previously, the CDC espouses the view that it is the intent of the person conducting the investigation that is crucial. They say that emergency response is an area that is considered to be practice. When the intent is to contribute generalizable knowledge, the activity is research. Otherwise it is public health practice. This was the view that was put forth to me by the public health officials with whom I spoke. The other view put forth is that it is the person or agency conducting the inquiry that determines the status of research or practice. Public health officials ‘practice’ and researchers and academics ‘conduct research’. This was what the academics that I spoke with told me. However, academics were less sure of their standpoint. One participant (#4) said: ‘Because all of SARS was so new, sometimes it all seemed like research’ Thus, I have empirical evidence that academics and public health officials each think that they have a fairly clear idea about the distinction between research and public health practice, but the groups do not agree. The same protocol conducted by these two groups of people may be research in one setting and not in the other. Perhaps as public health officials, ethicists and philosophers continue their dialog as described below in section D1, the nuances of these issues will become clearer.
The REB of the community hospital that I studied is accountable to the Board of Directors via the Medical Advisory Committee (MAC) of their hospital. The REB of the academic institution reports through the Medical Advisory Committee to the Board of Trustees (a group of people who provide financial oversight and are directly responsible for hiring/firing the CEO) which has the ultimate responsibility for the REB. (Personal communications). Importantly, the Chair of the academic REB felt free to access the Board of Trustees directly if necessary. At the community hospital, institutional conflict of interest (COI) arose, demonstrating why arm’s length interactions are recommended, but not always established or maintained. Pressure was forcefully applied to some REB members to approve certain protocols which hospital management and provincial authorities felt must be carried out. It was almost like a firing squad when one REB person was isolated and alone and battered with pressure to approve every protocol submitted without any changes. One person (participant #15), spoke about how she is not as vulnerable to this type of pressure, as most of her income comes from private practice. Moral strength was required says this participant. Approaching the media with the situation and being fired as a result of her attempt to protect hospital staff were both contemplated by participant #2.

The SARS outbreak highlights the potential for institutional COI. The revised draft 2nd edition of the TCPS continues to recommend a governance structure for REBs of arm’s length between REBs and their institutions, and my participants clearly showed why. The introduction to chapter 6 reads:

“A key goal in establishing an appropriate governance structure for research ethics review is to ensure that REBs operate with a clear mandate, authority and accountability, and that roles and responsibilities are clearly defined. REBs need operational independence to carry out their role effectively and to properly apply the core principles of this Policy – respect for persons, concern for welfare and justice – to their ethics review of research projects.”

And in the application of article 6.3, the TCPS continues: “Institutions shall respect the authority delegated to the REB. An institution may not override REB decisions simply to promote or prevent a
particular research project.” There is no provision, and nor should there be, for the administration of an institution to force an REB to approve a protocol that it feels is essential, but that the REB does not find ethically acceptable. However, institutional conflict of interest is not an easy problem to deal with. Many reforms for REBs have been proposed (accreditation, educational norms for REB members and, central REBs), yet none of them would solve the COI problem. Pressure to approve protocols that agree with the viewpoint of the institution will always be possible between the management of the hospital and the REB until REBs are not so closely linked with the research institution for which they review protocols. Even when REBs are not part of the research institution, as is the case with several commercial or co-operative REBs, financial transactions will still occur between the two, creating interdependence and leaving room for conflict of interest.

Many of my participants stated that they felt that some form of multi-centre review would have helped ease the burden and redundancy of the paperwork required for REB approval to multi-sites. REB members felt that a forum for consultation among various REBs about protocols that were submitted to many sites would have been helpful. The structure for all disaster related review of research proposals established after the Oklahoma bombing and described by Quick offered many advantages and should perhaps be emulated for other disaster or public emergency situations. First there was a single research ethics board for all proposals, no matter how many sites the protocol was implemented at thus eliminating redundant paperwork and allowing for consultation among members from various institutions. Second, this single IRB was aware of all proposals to be carried out and could implement a system whereby research subjects were protected from overburden by the approach from multiple researchers. Third, it was a single place for research volunteers to consult for information about protocols that were approved and ongoing. Fourth, it allowed for the merging of similar projects proposed for single sites and fostered a spirit of cooperation rather than
competitiveness. And lastly a single large database with all the demographics was created with data from all individuals affected by the emergency. This database was collected and cleaned once and available to all investigators conducting a research project approved by the IRB. These many advantages of a single coordinated oversight body that did more than just provide research ethics approval seems ideally suited to the conditions of a public emergency and we should follow the example of the University of Oklahoma’s initiative during other emergencies.

Surprising to me was the almost universal agreement that informed consent preparation was not difficult during the SARS outbreak. REB members did not speak about consent forms that needed many revisions. Because of the time that is normally spent on them in REB meetings, and the amount that has been written about how difficult it is to write a document that patients can understand, I expected that there would have been much more focus on them especially by REB members. Writing and reviewing consent forms is a familiar task and we have procedures to deal with them e.g., institutional consent templates. I suspect that the consent forms did not seem as important when REBs were worried about procedural issues such as how to adequately review all of the submitted proposals in a timely fashion given the circumstances of the outbreak and substantive issues such as seriously ill patients and unknown potential harms. Having said that however, researchers who submitted protocols to many REBs across the city did comment that many changes were required in the consent form particularly from the smaller centres. So while REBs did not find review of the submitted informed consent forms challenging, they did scrutinize them and request changes.

17.4 Limitations of the ‘Three Solitudes’ Study
The qualitative interviews took place from December 2007 to December 2008, and the SARS outbreak in Toronto occurred March – July 2003. Thus there was a four to five year gap between the experience of my interviewees and my questioning them about it. This recall bias may have affected what my participants remember about the experience. Several interviewees did mention that their recollection was not what they would like about certain details. One participant had almost no recall of anything different occurring in the REB process during the SARS outbreak. On the other hand, the experience of SARS was a very emotional one for most of these individuals. The time lapse between the outbreak and my interviews may have helped my participants to recover from any negative effects of this emotion and to focus more clearly on the events themselves. They had time to think about the experience and to process their thoughts and organize them in a way that made sense to them.

The second limitation of my study was the passive sampling strategy that was imposed on me by the community hospital. There were several individuals at this hospital that I wanted to contact, but the REB did not allow me to phone them and they did not respond to either the e-mail or the letter that was sent out by the REB. There were also several members of the REB who were approached by one of my participants, but who refused to be interviewed. These individuals said that the experience had been too traumatic for them and they did not want to relive it.

Despite these limitations, however, I do feel that my categories were rich and saturated and that conclusions can be drawn from the study. While I can never capture the perspective of those people that I did not interview, many of my participants were very passionate about the subject and were willing and able to provide me with many important and interesting insights into their experience.

17.5 Conclusion of the ‘Three Solitudes’ Study
Despite the limitations listed above, I believe I can draw conclusions from my work. I highlight two major conclusions that I believe are the highest priority to develop in this field. These are: 1) when REBs, researchers and public health are not effectively communicating during a public emergency, the work of each group is disrupted and 2) institutional conflict of interest occurred during the research ethics review of SARS-related protocols and may be amplified during a public emergency. Several minor conclusions include: 1) there is a need for a multi-site review structure that could be activated on short notice to review protocols related to the emergency situation; 2) the emphasis placed on consent forms by REBs may not be justified or appropriate; and 3) that once procedural issues are dealt with, critical timelines become easier to navigate. In general there was a fundamental lack of preparedness for research into outbreak-related issues by research ethics boards, researchers and public health officials and all these groups need to build preparedness plans that will facilitate research under these conditions. In particular, plans should be made for quick and thorough research ethics review of emergency-related protocols.
During the SARS outbreak, there were many different stressors and demands on the two REBs that I studied. Many changes were required because of the circumstances of the outbreak, the infection control measures, and the influx of SARS-related protocols. These changes occurred at the societal level, at the hospital level and at the REB level. At the REB level, each REB was required to adapt its procedures to accommodate the stressors. These changes were made by individual REBs without guidance, guidelines, standardization, or time for a lot of thought or planning about the changes and their implications. REBs did not consult with each other about these changes, and at least at the two centres that I studied, the changes that were implemented were quite different from each other.

In light of this and because it is never easy to change a large system such as the organization of REBs in Canada, I wanted to provide something that a single REB could do to facilitate approval of emergency-related protocols when the next public emergency occurs. I sought something that was meaningful and actionable and that would take into account some of the stressors that were prevalent during the SARS outbreak, including lack of availability of reviewers, inability to convene a quorum of REB members in a face-to-face meeting, and the infection control measures that were mandated by the Ministry of Health and Long-Term Care in Ontario. I also wanted an approach that would be easy to implement in the timelines available, that would provide a quick review as required by most emergencies, but that would allow reviewers to consider the many potential risks that might occur in a given emergency-related protocol. The ‘emergency review’ framework that is presented in the next part of this thesis is the result.
Part IV

‘EMERGENCY REVIEW’: A FRAMEWORK OF RESEARCH ETHICS

REVIEW FOR PUBLIC EMERGENCIES

A framework for research ethics review during public emergencies

Catherine M. Tansey MSc, Margaret S. Herridge MD MPH, Ronald J. Heslegrave PhD, James V. Lavery PhD


A shorter version of this chapter has been published by the Canadian Medical Association Journal and this longer version is printed with their permission.
CHAPTER 19: INTRODUCTION TO PART IV

19.1 A Global Problem

The current global outbreak of the swine influenza A1(H1N1) has once again focused international attention on preparedness planning for emergencies such as the SARS outbreak of 2003, the emergence of extremely-drug-resistant tuberculosis (XDR-TB), the threat of avian influenza, the terrorist attack on the World Trade Centre and the aftermath of Hurricane Katrina.\textsuperscript{202-206}

During the Toronto SARS outbreak clinical researchers noted that the need for research ethics board approval had resulted in ‘delays and missed opportunities’ for their clinical research protocols.\textsuperscript{65,207} Emergencies have illuminated the challenges for conventional research ethics review of combining speed and flexibility with intense scrutiny in review. These features, in combination, represent the precise challenge normally faced by REBs during emergencies. The World Health Organization (WHO) recently held a special technical consultation on “Ethics of research in influenza and other infectious disease outbreaks”\textsuperscript{208} in light of requests for guidance from research ethics committees around the world. One of the goals of the meeting was to provide WHO with urgently-needed guidance in this area, with specific focus on the question of whether and how prospective ethical review should take place for these activities.\textsuperscript{208}

In response to the need for speed and for in-depth scrutiny of the research proposals to be carried out in a public emergency, I have developed ‘emergency review’. It proposes a format of review that combines the speed of expedited or delegated review with special scrutiny as proposed by Levine \textit{et al.}\textsuperscript{15} in a manner that is proportionate to the risks and benefits of the proposed research project. ‘Emergency review’ is the focus of this part of the thesis.
19.2 Local Perspective

During the SARS outbreak in Toronto, there were several reasons why REBs could not meet in the regular way to review SARS protocols that were submitted to them. The most important of these were the restrictions imposed by the infection control measures that were mandated by the Ontario provincial government in order to contain the outbreak. Meetings of more than three people were not allowed in hospitals and off-site meetings were discouraged. Many regular REB members (e.g. outside legal consultants and community members) required by the TCPS for quorum in an REB meeting were not permitted into the hospital as only staff members were allowed entry. Many Toronto hospitals have more than one division and staff normally travels between them. This was not permitted during the SARS outbreak; staff had to choose the site at which they wanted to work and stay with it. Only individuals who had not entered any other division or hospital were admitted. Also at various times, REB members were in work or home quarantine and an occasional REB member fell ill with SARS. In these circumstances, meetings held by videoconference, might have been an ideal way to hold REB meetings, but the TCPS requires face-to-face meetings. As well, videoconferencing equipment was not available to REBs and their members during the SARS outbreak. Since then, the Interagency Advisory Panel for Research Ethics (PRE), the body charged with overseeing the development and evolution of the Canadian guidance document for ethical conduct of research involving humans, has ruled that videoconferences are acceptable on an occasional basis. The next best alternative meeting format is teleconferences, and despite the fact that the neither PRE nor the TCPS mentions them (in fact, they stress the importance of the non-verbal aspects of communication), teleconferences were used extensively during the review of SARS protocols.

The two REBs that I studied adopted quite different approaches to the review of SARS-related research protocols. At the community hospital, they developed what they called ‘crisis review’. They
tried to stay as close to the TCPS as they could. Under ‘crisis review’, five members with various expertise as mandated by the TCPS were present, i.e., five men and women, two with expertise in the methods and areas of research covered by the REB, one member knowledgeable about ethics, one member with knowledge of relevant law and one community member. Under ‘crisis review’, the decision reached had to be unanimous and there was no provision for appeal. Members not allowed into the building attended by teleconference. Using this format, the REB was able to review SARS protocols in a median of 20 days. While members told me about this format of review, I did not see evidence of this in the documentation that I was shown about these meetings.

At the academic centre, all but one of the protocols received expedited review. Expedited review was carried out as it normally is at this REB by the research ethics coordinators in consultation with the chair, but they were reviewed as soon as they were submitted. In order to review the more risky trial that required full board review, the chair used teleconferences to access the expertise that she felt was required. She had to call on experts from outside the Toronto area since all of the infectious disease physicians were either listed as co-investigators on the protocol, seconded to governmental posts to help control the outbreak, unavailable because of personal quarantine or illness or overwhelmed with clinical care of SARS patients. SARS protocols were reviewed and approvals sent out to investigators in a median of 4 days.

Each of these solutions has advantages and disadvantages. They both diverge from the TCPS guidelines somewhat, particularly in regards to the meeting format i.e., teleconferences, although the community hospital tried harder to stay closer to the letter of the TCPS document. Using ‘crisis review’ the REB at the community hospital may have sped up the time to a decision about protocols, although no data are available about the median time to decision prior to the outbreak. Similarly, it is
not known how much time the academic institution took to review protocols prior to the SARS outbreak. Anecdotally, 4 days seems much faster than under usual circumstances.

The treatment trial that was submitted to both REBs provides an interesting natural experiment. The trial was designed to evaluate treatment of SARS with ribavirin and was not expedited by either board; it was reviewed by outside expertise along with the chair at the academic institution (the chair had also participated in a full board discussion of this protocol at another institution where it was approved) and by the crisis review committee at the community hospital. It was approved at the academic hospital and not approved at the community hospital. Health Canada then rescinded its ‘no objection’ letter and so the trial was never undertaken. On this sparse data, it is impossible to know if the depth of the reviews were adequate. No records were kept as to what issues were discussed.

Thus there was no consistency across sites about how to review SARS-related protocols. Most of these protocols had not received any peer review as they were not funded by external sources that routinely review the proposals submitted to them for scientific merit. As a result, it was important that REBs thoroughly review the protocols both for scientific value and validity and also for ethical implication. The chairs and their REB members struggled with how best to respect both the guidelines of the TCPS and the infection control measures. Both decided that the infection control measures trumped the rules of the TCPS; they changed REB membership, both the number and expertise of reviewers were altered to suit the protocol under review; they changed meeting format; and they sped up review time, both time to initiate review and time to carry out the reviews were altered. Many of these changes that were implemented during the SARS outbreak are incorporated into the ‘emergency review’ process that is proposed below.
In this part of the thesis, I propose a new framework to guide departures from normal research ethics review during emergencies. It has its roots in the concepts of expedited review (relaxed procedural requirements), ‘special scrutiny’ (enhanced diligence) and proportionate review. It is also informed by the research described in parts I \(^7\) and III of this thesis.

### 19.3 Organization of Part IV

*Chapter 19 Introduction to Part IV*

This current chapter provides background information on the need for special procedures to provide research ethics review for emergency-related protocols submitted during public emergencies. It outlines the global problem, the need for a format to review research protocols during a public emergency and the types of research ethics review undertaken at two REBs in Toronto during the SARS outbreak.

*Chapter 20 ‘Emergency Review’ Background*

This chapter provides an overview of the literature that is relevant to research ethics review during a public emergency.

*Chapter 21 ‘Emergency Review’*

Here features of expedited review, special scrutiny and proportionate review are combined into a new procedure for research ethics review called ‘emergency review’ for use during a public emergency. It involves enhancing diligence of review, increasing procedural flexibility in a manner that is proportionate to the risks of the protocol under consideration.
Chapter 22 ‘Emergency Review’ Discussion

In this last chapter of part IV, I discuss some of the ramifications of implementing ‘emergency review’ along with some of its limitations. Ideas about how emergency review might be tested are presented as well as possible barriers to its implementation.
CHAPTER 20: ‘EMERGENCY REVIEW’: BACKGROUND

20.1 Literature Review

I searched Medline and Embase databases in order to capture any relevant articles in the scientific literature as well as Google Scholar and WorldCat (www.worldcat.org) for any relevant books and/or grey literature. These searches did not reveal any publication with a primary focus on guidance for research ethics review in emergency circumstances. Table 20.1 summarizes publications which shed light on some of the issues, and includes a commentary from the Wall Street Journal which highlights how worldwide research efforts were hampered during the SARS outbreak as a result of inability to obtain REB approval 209. While some issues from the ethics review of research proposed after the Oklahoma bombing in 1995 (e.g., the value of a centralized single Institutional Review Board model) are discussed by Quick 64, the report does not discuss details of the procedures or mechanisms used in Oklahoma. The chairperson agreed:

“to give an expedited full IRB review to all disaster-related research in order to deal fully with the issues of study design, appropriate timing, patient confidentiality, and method of victim and family member contact. Of utmost importance to the University, the City of Oklahoma City, and the DHSG [Disaster Health Studies Group] was the quality of the research to be conducted and the confidentiality of the subjects involved.” 64

They do not provide any detail about what ‘expedited full IRB review’ entailed.

Internationally, research during humanitarian emergencies has been characterized as “ad hoc” and “unregulated” 210. Médecins Sans Frontières (MSF) which provides humanitarian aid and conducts research in public emergencies 211, recognizes just three levels of research ethics review 1) full board review, 2) expedited review and 3) exempt from review 212. Reviews are carried out
electronically, discussion is by e-mail and the report is coordinated by the chair. Members meet face-to-face every eighteen months to discuss recurring and problematic ethical issues.

### Table 20.1. Summary of Literature Related to Research Ethics Review during a Public Emergency

<table>
<thead>
<tr>
<th>Author</th>
<th>Summary</th>
</tr>
</thead>
<tbody>
<tr>
<td>Whitley 209</td>
<td>highlights how worldwide research efforts were hampered during the SARS epidemic as a result of inability to obtain REB approval</td>
</tr>
<tr>
<td>Quick 64</td>
<td>discusses the value of a centralized single institutional review board (IRB) no details about the procedures or mechanisms used in Oklahoma are provided</td>
</tr>
<tr>
<td>Black 210</td>
<td>characterizes international research during humanitarian emergencies as “ad hoc” and “unregulated”</td>
</tr>
<tr>
<td>Ford 211 Schopper 212</td>
<td>recognizes three levels of research ethics review 1) full board review, 2) expedited review and 3) exempt from review 212 Médecins Sans Frontières (MSF) is conducting an increasing number of research projects during public emergencies 211</td>
</tr>
<tr>
<td>Exploratory Committee on Public Emergencies, a sub-committee of PRE 213</td>
<td>finds no specific guidance related to research ethics procedures during emergencies although a range of legal principles and general frameworks are cited</td>
</tr>
</tbody>
</table>

In 2006, PRE struck a subcommittee to investigate and propose amendments to the TCPS for research ethics review during public emergencies. As part of this work, the subcommittee reviewed a range of legal principles and general frameworks 214, and they found no specific guidance related to research ethics procedures during emergencies. They also consulted national and international documents such
as the *World Health Organization: Draft Project on Addressing Ethical Issues in Pandemic Influenza Planning*, the *Siracusa Principles*, and the Canadian *Emergencies Act* to confirm that these documents only permit derogation from their core principles in very limited and exceptional circumstances (e.g., public necessity and officially declared emergencies).

### 20.2 Elements of a Model of Research Ethics Review in Emergency Circumstances

#### 20.21 Substantive Methods

Three substantive methods were identified from the literature. These include expedited review, special scrutiny and proportionate review. All are described in more detail below.

#### 20.211 Expedited Review

Expedited review is a review process normally applied to studies of minimal risk with no novel or worrisome ethical issues. Although ‘expedite’ is widely understood to mean ‘speed up the process of’ etymologically the word denotes a removal of restrictions or impediments. In this sense, expedited review can be thought of as relaxing usual procedures of full REB review. This relaxation of restrictions generally makes expedited review faster and administratively less cumbersome than full REB review. While there is still some debate about the circumstances under which such relaxation of procedures should be applied, REBs generally employ expedited review when research protocols are deemed to present no more than ‘minimal risk’, admittedly a difficult standard to operationalize consistently.

#### 20.212 Special Scrutiny
Levine et al. argue that research protocols that present novel or ethically challenging questions, situations, and strategies or that pose a challenge to the status quo, warrant ‘special scrutiny’. Special scrutiny entails increased diligence in REB review, such as more frequent or sequential reviews, increased monitoring, and/or enhanced oversight of the informed consent process. As well, ‘special scrutiny’ recognizes that additional expertise may be required to review scientific or methodological aspects of novel proposals, or to assess the researchers’ account of the proposed study’s risk/benefit ratio, including the impact of the proposed research on the study community. They propose three criteria that may trigger special scrutiny: 1) the research involves initial experiences of translating new scientific advances to studies in humans, e.g., implantation of artificial hearts; 2) there is a known or credible risk for significant harm to humans as a consequence of experimental intervention without the offsetting potential for direct medical benefit e.g., sham surgery; or 3) the protocol raises ethical questions about research design or implementation for which there is no consensus or there are conflicting or ambiguous guidelines e.g., placebo trials where effective treatment exists.

20.213 Proportionality

The revised draft 2nd edition of the TCPS continues to explicitly call for proportionality as a guiding norm for research ethics review as did the original document: “Proportionate review is intended to reserve most intense scrutiny, and correspondingly more protection, to the most ethically challenging research.” For example, the first in human use of a new drug during an emergency would require greater intensity of review compared to a survey examining the impact of exhaustion on emergency service workers during the emergency. Conversely, protocols with minimal levels of risk for participants may require less scrutiny.
“A reduced level of scrutiny of a research project with minimal risks does not imply a lower level of adherence to the core principles. Rather, the intention is to reduce unnecessary impediments and facilitate the progress of ethical research.”  

20.22 Procedural Changes

During the qualitative study described in chapters 15 and 17, my interviewees told me about the changes that they made to their usual process of REB review. I kept track of these refinements and began to think about how these might be included in a framework that would improve research ethics review during a public emergency. These alterations included changing REB membership, speeding up the review time of SARS related protocols, and meeting via teleconference as discussed in section 17.22. Other changes such as varying assignment burden, extra monitoring and special need for scientific review arose from our reading of the literature and discussion among my co-authors and myself about the special circumstances that qualitative interviews had helped us to understand.

At the academic centre, most of the protocols were reviewed in an expedited fashion by the chair of the REB along with one of the research ethics coordinators. When a protocol did not qualify for expedited review, multiple teleconferences were used to contact outside expertise as many of the internal infectious disease (ID) specialists were not available. This occurred for several reasons: 1) most of the ID physicians on staff were named as co-investigators on the protocols and thus ineligible to review them; 2) many ID clinicians were very busy treating SARS patients; 3) some ID researchers were quarantined and occasionally ill with SARS themselves; or 4) several senior ID physicians were seconded away from their usual posts by the public health office to lend their expertise to contain the spread of the virus. Using this format, this centre reviewed protocols in a mean of 7 days (median 4 days) (see Table 16.1).
At the community centre, the REB membership was also changed, and the meeting format was altered as described in section 17.22. Community members were not allowed into the hospital and so they attended by phone. At this centre all but one protocol were reviewed using a new format that they devised and called ‘crisis review’. They stayed as close to the TCPS format as possible and formed a five member panel for each protocol. Panels varied for each protocol and the meetings were held much more frequently than usual. Intervals between meetings depended on the timing of protocol submission. The mean time to approval here was 21 days (median 20 days).

Many of the protocols submitted to these two REBs had not received external funding and thus had not undergone the peer review that normally accompanies such funding. REBs are charged with reviewing the ethical implications of the methods and design of research projects submitted to them as described earlier in Chapter 11. When emergency-related protocols involve more than minimal risk to the participants, ensuring scholarly review is particularly important given the uncertainties inherent in outbreak circumstances. These reviews could be undertaken by the REB when they have the relevant expertise or by some other expert body that would report back to the REB. Extra monitoring is also felt to be important for these protocols, although the feasibility of carrying out monitoring procedures remains untested. Because ID specialists were particularly affected by the outbreak, focusing their attention on an area of the protocol that most aligned with their expertise would be the best use of the available resources (methodologists reviewing only the methods section and laboratory specialists examining the basic science etc.) This assignment of review tasks was not tested during the SARS outbreak.

20.3 Process of Framework Development
Several areas where more flexible procedures might be employed were described to me by the REB members that I spoke with as discussed above. These ideas were discussed in several brainstorming sessions with my co-authors, in particular Drs. Lavery and Herridge. These helped to shape my thoughts about what should be included in the framework and many of the changes employed by the REBs were incorporated into our evolving thinking. I returned many times to the writing table, where I incorporated the ideas generated in each session into the manuscript. In January 2009, it was submitted to the Canadian Medical Association Journal. The review panel of the journal requested an expanded literature review and they wanted to see the paper take on a more international (less focused on Canada and Canadian regulations) flavour. These changes were made as requested and in December 2009, the framework was accepted for publication.

The proposed framework of ‘emergency review’ explicitly combines increased diligence, similar to that of ‘special scrutiny’ \(^\text{15}\), with enhanced procedural flexibility consistent with expedited review, in a manner that is proportionate to the perceived risks and specific circumstances associated with the research protocol. Although each of these guiding concepts focuses on a specific dimension of research ethics review, they have not been combined explicitly. Yet in emergency circumstances, it is precisely this combination of speed, depth and proportionality of review that is required.

‘Emergency review’ is triggered by the official declaration of a public emergency, as has been proposed for any exemptions to normal review procedures during emergencies in the revised draft 2\(^{\text{nd}}\) edition of the TCPS \(^\text{16}\). This restrictive application limits arbitrary demands on REBs and helps to reinforce the notion that any exemptions to normal research ethics review practices should be rare and should require a high level of justification. Protocols submitted to an REB under ‘emergency review’ are immediately assessed, either by the REB chair or, ideally, by an ‘emergency review’ sub-committee established in advance, for the risks associated with the proposed research, as well as the identification of important novelties or uncertainties that might require enhanced scrutiny. As part of this initial assessment, the urgency of the need for the potential information generated is evaluated and those projects reviewed first. Only research related to the emergency qualifies for emergency review; other research projects are reviewed in the usual way as time permits, assuming an REB quorum can be reached.
21.12 Enhancing Diligence of Review

Complex protocols and those assessed to involve a high level of risk to the participant or to the community are assigned a greater number of principal, or ‘in-depth’ reviewers, representing the relevant expert perspectives. The REB chair is free to call on non-REB members for special expertise. Reviewers could also be directed to focus their attention on those aspects of the proposal that aligns directly with their expertise and to limit their reviews to very specific questions. Such an approach not only enhances attention to ethically relevant aspects of the study, but also improves the availability of REB members for other time-sensitive reviews related to the emergency. The use of non-REB experts, in addition to REB members, provides redundancy in the review, a key measure for enhancing scrutiny.

Research submitted to an REB for review during an emergency may not have outside funding and thus may not have been peer reviewed for scientific merit. The REB may decide that there is a greater than usual requirement for both scientific and ethical evaluations in emergency circumstances, such as whether sufficient animal or preliminary human safety data are available for a new application of an existing therapy. REBs could also require heightened monitoring of a proposed study as a means of enhancing ongoing assessment of the risks and potential benefits. This is particularly appropriate in protocols where the understanding of the risks and benefits of a novel intervention are expected to evolve quickly, as would be the case in a treatment trial of an acute, life-threatening disease. Early detection of toxicities or other harmful effects of the research intervention could help to reduce research-related harms by making adjustments to the protocol, or ending the intervention, if necessary.

21.13 Increasing Procedural Flexibility
Rather than providing a broad suspension of the usual procedural requirements of national and international guidance documents, ‘emergency review’ requires that any relaxation or alteration of these requirements be proportionate to the complexity and urgency of the emergency and to the risks posed by the specific research proposals under review. Depending on the volume of submissions to the REB, protocols related to the emergency are either reviewed individually by the REB chair, or his/her delegate – as is normally done in expedited or delegated review – or examined by the chair and/or a specific triage committee, and prioritized according to the applicable substantive ethical guidelines. Where protocols are deemed to be beyond minimal risk, judgement is required to determine the necessary number and expertise of reviewers. The aim of the proposed procedural flexibility is to enhance scrutiny, wherever possible, as well as to ensure timeliness of review.

21.131 Procedural Requirements that May be Altered

The unique panel of REB reviewers for each protocol is selected for their expertise relevant to the current protocol i.e., reviewers are decided on a per protocol basis and each protocol has a unique panel of experts review it. The chair or an ‘emergency review’ sub-committee that was established in advance of the emergency evaluates each protocol for level of risk when it is received and based on their experience and judgement assigns the appropriate reviewers to it. A more risky and/or complex protocol is allocated to a greater number of reviewers with more diverse areas of expertise than one that is simpler and less risky. Some protocols may require evaluation by several members of the public or patient representatives. Thus increased diligence is accomplished by the redundancy of reviewers with multiple perspectives.

Because every protocol is not read by every REB member (as is often the case) the burden to reviewers is less than it might otherwise be; competing demands may be reduced. This leaves
members available to target their review very specifically to the areas where they can be most efficient and effective in their review.

Meeting format and frequency also varies. Teleconferences or videoconferences accommodate reviewers’ schedules and possible restrictions on reviewers’ mobility, a circumstance that prevented many REB meetings when isolation and quarantine procedures were applied during the Toronto SARS outbreak. Many REBs normally meet monthly, but this frequency might not be enough when protocols are being submitted rapidly. For instance at the community centre, the first four protocols were received on April 7, April 22, and April 26 and May 8th. Under ‘emergency review’ four short meetings would have been held shortly after each submission. If the emergency is less complex than the SARS outbreak or if the nature of the submitted research is judged to be less urgent, bi-weekly meetings could be scheduled.

Because under ‘emergency review’ protocol review panels are unique and do not usually require the full membership to be present, it is possible to both initiate and carry out a review much more quickly than usual. Submissions occur by e-mail, whether or not this occurs under normal circumstances. Focused specialist reviews could be available within a short time, perhaps 48 to 72 hours after the request was sent out by e-mail for very complex protocols and more quickly for proposals where the risks are less and/or the benefits are judged to be greater. There is also a streamlined reporting format in place where emergency-related responses to researchers are formulated before others. During the SARS outbreak, both the academic centre and the community hospital processed SARS-related protocols before any others. The academic centre processed others as time permitted while the REB at the community hospital was closed to other work.

Scientific peer review is expected to be performed by Canadian REBs under the guidelines stipulated by the TCPS. Many protocols that are submitted to the REB under normal circumstances
have received some form of peer review, and so may not require an in-depth scientific review once the REB has ascertained that this has been carried out by another agency, usually a funding body. However, most of the protocols that were submitted during the SARS outbreak had not received any outside funding as so had not been peer reviewed. Thus in-depth scientific review for validity and social and scientific value may be required more often under emergency conditions. The scope of this review is related to and proportionate to the risk of the protocol to participants, the complexity of the protocol and the controversial nature of the proposal.

During emergency conditions, it may be difficult for researchers to predict and REB members to assess the level of future risk that results from a particular research proposal. New knowledge may be evolving quickly as a result of world-wide information sharing over the internet. In some complex protocols, particularly those involving new drugs and/or new pathogens, it may be difficult to know ahead of time the risk to both research participants and to research staff. Thus REBs may wish to monitor this type of research more closely than is usual. They may wish to see reports of recruiting speed or staffing safety more frequently, perhaps monthly or even weekly if events are occurring quickly. This is an option that is always available for REBs to request, but may become more important under emergency conditions.

Table 21.1 provides a summary of the ‘emergency review’ framework and its application. ‘Emergency review’ does not remove procedures, it is not about decreased scrutiny, but rather is enhanced through a process that is flexible and tailored to the protocol at hand.
<table>
<thead>
<tr>
<th>Procedural requirements that may be altered</th>
<th>Procedures that may increase diligence</th>
<th>Factors relevant to diligence and speed of review</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>REB membership</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Variable number of reviewers</td>
<td>• Redundancy of review</td>
<td>• Complexity of protocol</td>
</tr>
<tr>
<td>• Public representation changes according to the issues raised in protocol</td>
<td>• Multiple perspectives</td>
<td>• Assessment of risk</td>
</tr>
<tr>
<td>• Expertise of reviewer varies by protocol</td>
<td></td>
<td></td>
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<tr>
<td><strong>Review time</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Time to initiate review occurs within hours of receipt of protocol</td>
<td>• Prioritization of relevant protocols</td>
<td>• Urgency of the proposed research</td>
</tr>
<tr>
<td>• Time to carry out the review changes according to the issues raised in protocol</td>
<td>• Reduction of competing demands on REB members</td>
<td>• Risk–benefit ratio</td>
</tr>
<tr>
<td>• Streamlined format for communicating with researcher decreases waiting time</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Assignment burden for reviewers</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Expert reviewers review only protocols directly related to their expertise so that overall burden of review may be reduced</td>
<td>• Reduction of competing demands on REB members</td>
<td>• Complexity of protocol</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Urgency of the research</td>
</tr>
<tr>
<td><strong>Meeting format</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Face-to-face or virtual depending on availability of reviewers or physical limitations imposed by the emergency</td>
<td>• Redundancy of reviewers</td>
<td>• Complexity of the emergency</td>
</tr>
<tr>
<td></td>
<td>• Multiple perspectives</td>
<td>• Urgency of research</td>
</tr>
<tr>
<td><strong>Scientific peer review</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• May or may not be needed depending on what review has already occurred</td>
<td>• Assessment of value and validity</td>
<td>• Risk of protocol to participants</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Complexity of protocol</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Controversial nature of proposal</td>
</tr>
<tr>
<td><strong>Monitoring</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• May be increased where risk is high or uncertain</td>
<td>• Ongoing assessment of risks and benefits</td>
<td>• Complexity of protocols</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Difficulty in assessing future risk</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Risk to participants or research staff</td>
</tr>
</tbody>
</table>

Note: REB = research ethics board.
The main innovation of ‘emergency review’ is the merging of three established guiding concepts for research ethics review procedures – 'special scrutiny', expedited review, and proportionate review – into a single framework for emergency circumstances. ‘Emergency review’ responds to the three main policy challenges for research ethics review, which are likely to be magnified in emergencies. First, REBs and their institutions are responsible, and must be accountable for, thorough and careful review of research proposals. Second, especially in emergency circumstances, failure to conduct a high quality review with sufficient speed can result in lost opportunities to gain critical knowledge. For example, in the treatment of unknown or poorly understood pathogens, our ability to resolve important clinical questions quickly may be a key determinant of case fatality rates for an infectious disease outbreak. And third, in all cases, the level of scrutiny and flexibility in procedural standards must be proportionate to the risks and uncertainties involved.

Core principles as set out by the TCPS (or other guiding documents or relevant legislation in jurisdictions other than Canada) are not meant to be altered with this procedural relaxation. This is rather a procedure to facilitate their application in the unusual circumstance of a public emergency. It is not unusual for the application of the same core principles in a different context to result in a different outcome. 221 Risks and benefits, particularly those to the community are likely to be different during a public emergency.

‘Emergency review’ is not a framework of substantive ethical principles, or a “how-to” guide for REBs to respond to individual emergencies. Rather, I view it primarily as a tool to help REBs and
institutions to plan their emergency procedures in ways that will ensure the best fit between the procedures of research ethics review and the special demands imposed by emergency circumstances. As with any new policy model, the merit of ‘emergency review’ needs to be determined in the application and evaluation in real emergency situations. In many countries, regulation of research and research ethics review falls to a national body, thus the acceptance of this framework might need to be incorporated into national research guidelines. Advance planning and institutional support can help REBs to have the appropriate documentation and evaluative strategies in place in the event of an emergency to permit the necessary data collection and evaluation.

There are several limitations to ‘emergency review’. First, it does not help with the initial assessment of risk and urgency of the research. REB chairs need to use their judgment and experience to set priorities. Perhaps the values judged to be the most important at individual institutions should be explicitly spelled out ahead of time. Second, ‘emergency review’ does not help with the need for multi-centre review to cut down redundancies when a project is to be performed at multiple sites. Third, it will not protect participants from being approached multiple times for projects (research or outbreak investigation) that are coordinated out of other institutions or by public health officials. Fourth, it does not help REBs deal with the problems of non-emergency-related research, be they new projects that require review or ongoing ones that require monitoring, and especially interventions that might be required as a result of serious adverse events.

Despite these limitations, there is still value to be gained from using ‘emergency review’. It could be used at a single site or to perform a multi-centre review. The principles behind it could also be used to modify the procedure for use under usual conditions i.e., so that it complies with the TCPS when used in Canada. Expedited review could be carried out as usual, protocols judged to be just slightly more than minimal risk, could be reviewed by the required five individuals with the relevant
expertise, full board review could review protocols that are more than minimal risk and very risky or novel protocols could have extra people called in to aid with the review. This would be done on a per protocol basis so that reviewers’ expertise is very tailored to the protocol under review.

Similar tools to enhance the quality and reliability of research ethics review have been applied to good effect. For example, the Alberta Research Ethics Community Consensus Initiative (ARECCI) has developed a tool that assigns a numeric estimate of risk in each research proposal. Although this tool was not designed for public emergencies, it might be used as part of ‘emergency review’ to quantify risk in emergency-related protocols and so make their triage a little less subjective.

The emergency review process might prove to be most useful in those studies in the grey zone between those that most REBs would agree should receive expedited review (e.g., chart reviews) and those that all agree require full board (or perhaps even more scrutiny) such as treatment trials. There were three protocols that were reviewed at both centres that I studied (3a/1c [chart review], 9a/4c [seroprevalence in health care workers], and 14a/2c [the CSRN studies described in some detail earlier]). The seroprevalence study and the CSRN group of studies might both have benefitted from more in-depth review than either of the two centres was able to provide. Perhaps ‘emergency review’ might have been able to fulfill this role.

The revised draft 2nd edition of the TCPS was drawn up by PRE after the SARS outbreak in consultation with experts from across Canada. The authors of a new section called ‘Research Ethics Review during Publicly Declared Emergencies’ consulted the people who had experience with research ethics review during the SARS outbreak as well as other stakeholders and the current literature. Article 6.20 stipulates that:

“In concert with their researchers, institutions and their research ethics boards should develop emergency research ethics preparedness plans. Research ethics review during emergencies may follow modified procedures and practices.”
The application of this article allows for “reasonable adjustments to address the timing, locale, expertise, form and scope of review and the holding of REB meetings” (without any clarification of what is ‘reasonable’). This article thus recognizes the potential need for procedural flexibility in response to the demands of specific emergency circumstances. The new section emphasizes that the substantive ethical requirements of the TCPS are expected to be applicable during public emergencies; REBs are cautioned to “be vigilant and exercise due diligence in respecting ethical principles, procedures, and the law in effect during the emergency”. However, the new section stops short of outlining a specific procedural framework, leaving this process to the discretion of REBs and their institutions. 

Health Canada has adopted an approach that emphasizes ‘time-sensitive’ review, and in response to the latest H1N1 influenza outbreak in Canada, the Public Health Agency of Canada has developed a pilot project titled: Streamlining Ethics Review of Multi-Centre Pandemic Influenza Research. But these approaches do not explicitly address the need for enhanced scrutiny during unusual circumstances, and may not be applicable to all public emergencies, and represent a considerable departure from the procedures normally followed by institutionally-based REBs, making their widespread application doubtful. Thus several federal agencies have taken preliminary steps to outline guidelines that are useful during a public emergency, but none outlines a specific procedural framework.

During the SARS outbreak, in at least one institution, institutional conflict of interest resulted because of lack of arm’s length between the REB and the management of the hospital. While this procedural innovation will not change the lack of arm’s length between these bodies, once procedures
are written into policy and approved by the board of the institution, perhaps it will be more difficult to apply pressure when approved policy is being adhered to.

Emergency review may also represent a useful framework for improvement to research ethics review procedures more generally. Pilot testing emergency review under normal circumstances may help prepare REBs for emergencies, but it may also offer insights into whether this strategy truly can improve both the quality and efficiency of review. If so, ‘emergency review’ might prove to be useful beyond emergency circumstances.
CHAPTER 23: CONCLUSION OF THE THESIS

In part I of this thesis, I report on the results of the outcome study conducted during the SARS outbreak in Toronto. Part II is an analytic reflection of the ethical issues encountered during the conduct of the SARS outcomes study. Part III discusses a file review called ‘Two REBs’ whose goal is to determine the type and number of research projects submitted for research ethics review about the SARS outbreak and its impact as well as a qualitative inquiry called ‘Three Solitudes’ with the objective of understanding the impact of the SARS outbreak on research ethics review of SARS-related protocols. Part IV presents ‘emergency review’, a framework to guide departures from normal research ethics review during emergencies. In this chapter, I discuss what makes my research unique and the contributions that I make to our knowledge about how research ethics review occurred during the SARS outbreak. I also elucidate some of the limitations of the work and some of the areas that should be developed further in order to move the field forward.

A. Main Contributions of this Thesis

This study is innovative in several ways. First there is no literature describing research ethics review during an outbreak of infectious disease. To fill this gap, I have developed a theory about how researchers, research ethics boards and public health officials interacted during the outbreak which I have called ‘Three Solitudes in Research Ethics Review during the SARS outbreak’ (Figure 17.1). Second, there is no guidance in the literature about how to undertake the review of an emergency-related protocol during a publicly declared emergency. To fill this gap, I have developed ‘emergency review’ for use under these circumstances. The series of inquiries is unusual in that it uses several
methodologies, which were developed and are often used in different fields, i.e., an observational study using a method from clinical epidemiology, a reflective analysis of the type undertaken in bioethics, a grounded theory study based on a method developed in the social sciences and a translational study that uses information gleaned from all of the previous studies to propose a strategy to help with research ethics review during an emergency. These two major contributions of the thesis and their implications are discussed below.

A1. The Three Solitudes Theory

The natural experiment that was the SARS outbreak revealed that researchers, REBs and public health officials (the players in my theory) do not routinely communicate with each other. Each operates in their own world. Within the crisis situation, this fundamental isolation was exposed. When these players were forced to interact with no time to develop healthy working relationships, and given the stressors described above (infection control measures; the fuzzy boundary between public health surveillance/outbreak investigation and research during a public emergency; and pressure to approve protocols quickly), interactions between the groups were not always collegial. Some researchers tried to manipulate REBs to more quickly approve their protocols; some public health personnel tried to coerce REBs into approving their proposals; and public health officials and researchers at times obstructed each others’ work.

There are two uses to which such a theory might be put. First, the findings may be used to understand the situation and so realize where efforts are required to improve it. This is, perhaps a positivist use of the theory, where the results are taken as revealing the truth about what occurred in the situation and moving forth to ‘correct’ or ‘improve’ it. In this case, the importance of improving interactions between the three groups could be highlighted. Preparedness planning for research ethics
boards might take into account my results and work toward mitigating the negative interactions that occurred. REBs are always working to improve their relationship with researchers and many are trying to work as a team so that all research proposals strive to protect their research participants as much as possible. The relationship between hospital-based REBs and the public health department was particularly problematic. Several strategies for improving public health research ethics dialogue and education are outlined below in section C1.

Secondly, a theory can be tested and applied more generally to other circumstances. For example, several REBs responses to an unusual occurrence might be examined. In order to learn what an REB does when faced with an unfamiliar type of protocol, a biomedical REB might be examined when reviewing a qualitative project or public health protocol. Since there would not be the time urgency seen in the SARS outbreak, the interactions between the investigators might be examined and the steps taken by the REB to understand the protocol be parsed apart. The results from such a study could be used to further understand and modify REB strategies when faced with such a circumstance. Alternately, an investigator familiar with group dynamics might investigate the manipulation and coercion that I have incorporated into my theory and expand on the factors that allow for such negative interactions.

A2. The Emergency Review Proposal

Many of the REB members that I interviewed commented on the fact that during the SARS outbreak, they were unable to follow the guidelines set down in the TCPS in the way that they usually do. While this was not a core part of the theory that I generated, it was certainly a part of the stressors that were felt by both REBs that I studied. I postulated that if some of these stressors could be reduced, the uncertainties about how to proceed would be diminished. (In fact, this is a core premise
of preparedness planning.) The revised draft 2nd edition of the TCPS goes much further than the previous version in recommending proportionate review of research protocols. In response to this, to the uncertainty articulated by my interviewees and to the need for speed and for in-depth scrutiny of the research proposals to be carried out in a public emergency, my co-authors and I developed ‘emergency review’. It proposes a format of review that combines the speed of expedited or delegated review with special scrutiny as proposed by Levine et al. in a manner that is proportionate to the risks and benefits of the proposed research project. It was demonstrated during the SARS outbreak, at least at one REB, that overnight approval of a research proposal is possible when priorities are changed and there are not competing demands on the REB’s time. The ‘emergency review’ format may prove to be useful not only under these circumstances but also under usual conditions. It is the first time that such articulation of a strategy for research ethics review during a publically declared emergency has appeared in the literature and we hope that it will begin a dialogue on the advantages and disadvantages of such a scheme and that others will propose refinements and modifications to improve it. The challenges in testing this model of review are discussed below in section D3.

B. Limitations

I have discussed the limitations of the individual inquiries in the relevant sections of the thesis. Here I discuss the overall limitation of the thesis; the weaknesses and the implications of these weaknesses.

There are two limitations to the series of inquiries. The first is that I focus only on SARS-related protocols as opposed to all research that was submitted to REBs during the outbreak. This was done for the purpose of feasibility. Many other protocols must have been submitted, especially to the busy academic REB, and some were reviewed as time permitted, but they were not the priority. The
effect of this delay was not studied at all. The REB at the community hospital was closed to all protocols other than those related to SARS. I do not know how many projects this may have delayed. I also did not study the effect of the outbreak on any research projects that were underway at the beginning of the outbreak. Given the restrictions on patients entering the hospitals, and the reluctance of the public to enter hospital premises, many projects must have been abruptly discontinued. While this may have just delayed some research protocols, alternate arrangements to meet patients must have been made, particularly for drug trials, where it is important for patient safety and adequate treatment that drug regimens not be interrupted. Anecdotally, I heard about research nurses meeting patients in the parking lot, researchers renting hotel space to meet with patients and alternate sites being set up for the research pharmacy. None of these were studied in my series of inquiries, and thus I am not able to draw any conclusions about these important aspects of the outbreak on research or on REBs.

The second limitation of my thesis relates to the fashion in which it evolved. I did not begin with the goal of studying REBs. After each step in my research journey, I was left with a series of questions. Because of the type of question that was generated, I was constrained in my methodological choices. For instance, after the SARS outcomes study, and only being practiced in quantitative methods, I developed the file review and asked mainly quantitative questions. This seemed reasonable given that questions like the number of protocols reviewed, type of review, and time to approval are standard metrics often quoted when describing an REB. However, at the end of this study, I had generated more questions than answers. Since I had minimal knowledge about the operations of REBs, I knew that I had to speak with people who were more knowledgeable than I about this matter. Since I wanted to do this in an academically rigorous fashion from the beginning of my knowledge gathering, I chose grounded theory, which is well suited to investigating a situation without a lot of prior knowledge. In fact, that might be seen by some as an advantage; I could not be
led astray by prior preconceptions. Each step followed the previous one and I seemed bound by it. This may have hindered my ability to focus more broadly on the issues and may have narrowed my vision.

Were I to design a study now, knowing what I have learned from the present series of inquiries, to investigate the effects of the SARS outbreak on REBs, I would do one of two things. I would either narrow my focus to the interactions between hospital staff (both researchers and REBs) and public health or broaden my lens to include more REBs and focus on the procedures that each REB developed to handle the influx of SAR-related protocols. Had I chosen the former option, I would have spoken with many more public health workers to obtain the perspective of others as well as the physicians involved. If I were fortunate enough to have been working on the project at the time of the outbreak, I might also have observed firsthand some of the interactions among these groups. I would have tried to understand what conditions fostered good working relationships among them. I would also have tried to understand how all of these professionals viewed the distinction between research and practice/outbreak management and surveillance under these circumstances. Had I chosen the latter option, I would have studied many REBs and examined not only the procedures that were used to review emergency-related protocols, but also the process by which they were arrived at. I might also have looked at the reporting structure and the internal dynamics of the boards to understand what it was about each board that fostered cooperation or lack thereof between staff members. I might have tried to understand if there was something about the institution, or perhaps the personality of the chair that rendered research particularly valuable or created an atmosphere where research was facilitated. Either of these two studies would likely have provided different results that those that I was able to obtain. Perhaps my studies were required to realize that these others might
have provided a deeper understanding of the functions and procedures of an REB under the stress of an outbreak.

C. Conclusions

Despite the limitations listed above, I believe that I can draw conclusions from my work. I could draw many conclusions (e.g., that consent forms are not as important as the amount of time spent on them by REBs would suggest, that once procedural issues are dealt with, critical timelines become easier to handle or that there was a fundamental lack of preparedness for the outbreak), but I’ve chosen to highlight just three that I think are the highest priority to provide further development in this field. Two of these are a direct result of the theory that was developed in the ‘Three Solitudes’ study. These are: 1) that when REBs, researchers and public health are not effectively communicating with each other during a public emergency, the work of each group is disrupted and 2) that institutional conflict of interest occurred during the research ethics review of SARS-related protocols and may be amplified during a public emergency. The third conclusion was a minor one from the ‘Three Solitudes’ study but it was mentioned by almost all of my participants. This is the need for a multi-site review structure that could be activated on short notice for the review of protocols related to the emergency situation. It was relevant to the SARS outcome study and at the end of the analytical reflection, I concluded that this was an important aspect of emergency preparedness planning that needed to be developed.

C1. Communication during a Public Emergency

Effective communication is critical during a public emergency. REBs, researchers and public health were forced to communicate with each other, but because they do not speak a common
language, misunderstandings, hard feelings and detrimental effects on their work occurred.

Participant #6 speaks of a disagreement between researchers and the community hospital REB that may have led to a delay in the collection of data that the researcher saw as critical to ‘population-patient care’ (Participant #6). Participant #19 discusses the negative impact that researchers had on her work in trying to control the outbreak when they denied her the access that she felt she needed to patients’ medical records.

Researchers, REBs and public health officials did try to build bridges between their worlds. Researchers spoke about phoning the REB and discussing their projects with the chair and asking for and getting quick turn around on their proposals. REB members spoke about how they saw themselves as facilitators (at least at the academic centre) and how they tried to ensure that the ethical review of research was not an impediment to important research projects. Researchers spoke about daily conference calls set up during the SARS outbreak, to discuss patient care, research projects, and new cases that they had been briefed about by public health. Thus there was some collegial communication between the players in my theory, and these links need to be strengthened in order to facilitate ongoing interaction between these groups of people.

Many of the problems of REBs and IRBs have been framed as inefficiencies particularly in public health. 163

“public health practice activities cannot be effectively carried out in a timely manner if they are subjected to the considerable administrative burdens associated with an IRB review . . . requiring emergency responses to include the traditional development of a written protocol and IRB review is not practical nor would it be in the best interests of either the individuals or the community affected by the problem because the resulting delays in identifying the nature and magnitude of the community health problem and in instituting control measures to take such steps would frequently result in excess disease and death.” 163

The spectrum of inefficiency may run from inconvenience to disruption to obstruction. Under usual conditions, inefficiencies in the system are just inconveniences or mildly disruptive. However, during
a public emergency, these same inefficiencies are obstructive to the completion of the required tasks in the required time. A delay in halting an outbreak may mean further transmission and higher mortality. Resolution or amelioration of the problems of communication and of inefficiency may allow the goals of researchers, REBs and public health officials (i.e. the generation of new knowledge in a way that protects participants) to be achieved.

C2. Institutional Conflict of Interest

I learned from the ‘Three Solitudes’ study that coercion and manipulation were part of the interaction strategy on the part of some researchers and public health officials as they dealt with REBs during the SARS outbreak. Both of these groups were able to access those above the REB level on the organization chart of the hospitals to apply pressure to approve protocols. The governance structure of research ethics review in Canada, in particular the reporting structure of REBs to their institutions allows for these conflicts of interest (COI) to be felt and to be disruptive to REBs.

Discussion of governance issues of research ethics review is ongoing in Canada. In 2004, a group of Canadian research ethics experts met to discuss the governance of research involving humans in Canada. Another meeting in 2005 attended by the Royal College of Physicians and Surgeons of Canada, the Association of Universities and Colleges in Canada (AUCC), Health Canada and the three Canadian federal research granting agencies (CIHR, SSHRC, and NSERC) again took up these issues. They “established an expert committee to look into a range of governance models for the oversight of ethics in human research and to explore issues including implementation and funding.” This expert committee became known as the ‘Sponsors’ Table’ and received briefings from the National Council on Ethics in Human Research (NCEHR), the Interagency Advisory Panel on Research Ethics (PRE), the Association for the Accreditation of Human Research Protection
Programs (AAHRPP), and the Canadian Council on Animal Care (CCAC). They issued a final report in 2008 in which they conclude that:

“the current system has evolved as far as it can in the absence of a national plan and set of standards and it is now time to bring a coordinated and comprehensive system of overall participant protection to bear in order to maximize efficiency and reduce burdens to the extent possible.”

To further this end, they recommended “the establishment of a comprehensive system of research participant protection in Canada, together with the creation of a Canadian Council for the Protection of Human Research Participants”. Thus many experts agree that our Canadian governance of research ethics review is in need of restructuring, but the proposed solution is expensive and may not be supported by the three research councils. Initiatives like those discussed above need to continue until a solution to these problems is found.

C3. A Form of Multi-Centre Review is Needed

The topic of multi-centre review recurred in many of the inquiries in my thesis. Researchers, REB members and public health officials agreed that some mechanism to accomplish this would be a step forward and that this would be particularly useful during a public emergency. Several types of central REBs are being tried in Canada such as the provincial board in Newfoundland and Labrador, OCREB for cancer trials in Ontario and the physicians board in Alberta. However, those currently operating may not have a procedure in place to quickly react to the circumstances of a public emergency. For example, some of the current central REBs discussed earlier, such as OCREB negotiate the legal contractual agreement on a per protocol basis (personal communication). While there were relatively few multi-site studies submitted to the two REBs that I studied, some of these required approval from many REBs. For example, the SARS outcomes study was submitted to
twenty-two REBs and the chart review for the descriptive study of clinical features of SARS was submitted to eleven REBs. Negotiating legal contracts for each of these centres would be impossible to organize in the short time required in an emergency situation.

Several multi-centre research review strategies have been suggested. The most sweeping change is suggested by Emanuel et al. who propose “the establishment of a system of single review of multi-site research with liability protection for local institutions.” This paper exclusively pertains to the United States, however similar changes might be suggested in Canada or at the international level. Whatever the scope of the system, it would need to be mandatory and would likely require legislation by all participants. While perhaps this approach is the most effective at reducing “repetitive and time consuming review of multi-site proposals” and overcome the problem of legal liability, it would be expensive and difficult to operationalize, organize and implement.

Collogan et al. advocate a collaborative approach within a specific geographic region similar to that adopted after the Oklahoma bombing which was described previously. This format would not only help with the redundancies of the paper work of research ethics review but could oversee the potential problem of overburdening potential participants as one central REB is aware of all research that is being conducted about the emergency. This central REB could also promote collaboration between researchers, perhaps decreasing competition for funds allotted for research about the emergency when researchers chose to work together on common projects and thus use fewer resources for equal or greater knowledge generation. It should encompass a regional area, the appropriateness of which will vary according to the emergency. This approach has the advantage of being tailored to the emergency and does not require legislation beforehand. Perlman however, suggests that academic health centres may not be the most appropriate REB to take on this role. He advocates public health units or state units of health REBs be used instead, stating that:
“such research may be better reviewed at IRBs operated by state departments of health . . . as they must have experts who understand the differences between public health practice and research and who have familiarity with the ethical and regulatory requirements of waiver of informed consent, secondary use of public health data for research purposed, and other considerations unique to public health.”

Perlman also recommends that every state (the same might apply to Canadian provinces) have its own IRB and that each of these has standard operating procedures (SOPs) in place that could quickly review protocols during a public health emergency. I would add to this that the SOPs should have a mechanism such as that described in the ‘emergency review’ part of this thesis to ensure that protocols are reviewed in adequate depth. The exclusive review of all emergency-related research however, may be problematic where funding has been provided to researchers by the public health agency, creating a conflict of interest if their own REB is used to approve these protocols for use at many sites with no further scrutiny. It may also be problematic for review of biomedical proposals. While I would agree that some hospital centres may not have the required expertise for public health research, some knowledge about clinical research would be required on the designated REB since protocols may investigate new pathogens and their treatments, physical and mental injuries resulting from the emergency and/or the impact of the emergency on many different groups. University REBs have perhaps the broadest range of experience as they are used to reviewing biomedical research, social science proposals and, in those that have schools of public health, public health protocols.

A pilot project was set up by the Public Health Agency of Canada (PHAC) during the H1N1 pandemic as a result of a grass roots initiative by several REB chairs to streamline review of pandemic protocols. (personal communication: R. Heslegrave) For each multi-centre protocol, a lead site was identified. The lead site reviewed the protocol with the assistance of several external experts with knowledge relevant to the protocol who join in the discussion in a virtual manner. Their discussions are posted on a secure web site that is available to all other centres participating in the
protocol. Any other REB could then ‘tune in’ to this web site and listen to the discussion. Thus these expert discussions about the protocol are accessible and need not be repeated at other REBs. This type of initiative might be particularly useful where there are many small local outbreaks, but where larger scale emergency situations are not reached as was the case with the H1N1 pandemic. This mechanism to facilitate research ethics review of public emergency protocols has not been fully evaluated yet as the pandemic waned before a sufficient number of protocols were reviewed, as was the case of my proposed ‘emergency review’

D. Future Directions

I have identified three areas for further development: 1) to promote research ethics dialogue and education between researchers, REBs and public health, 2) to incorporate my insights into guidance documents and 3) to test the ‘emergency review’ process before implementation. The need has become pressing as public emergencies such as the current H1N1 swine influenza pandemic will continue to occur as noted by Dr. David Satcher in the introductory remarks of this thesis.

D1. Promote Public Health Research Ethics Dialogue and Education

The crisis of SARS has helped bring the three solitudes of REBs, researchers and public health a little bit closer, at least in Canada. There has been more money available for infection control within hospitals. Also, in response to the Nayor report, the Public Health Agency of Canada (PHAC) was formed in 2004, and was confirmed as a legal entity in December 2006 by the Public Health Agency of Canada Act. However, when I asked researchers and public health officials if they thought that the agency would make the situation more workable should another outbreak or pandemic occur, they unanimously said that they did not think so. They spoke of another layer of
bureaucracy added to the system. They also spoke of a system that hasn’t found its niche yet; hopefully that will come with time.

We need to take this opportunity to clarify the roles of public health, public health research, public health research ethics and in particular, public health research carried out in a hospital setting for the next public emergency. Participant #19 spoke of the need within public health to develop its own thinking about the ethical issues encountered in their day-to-day practice:

> I mean it’s very interesting and I think it comes back to what we were talking about at the public health ethics conference ... at public health practice we don’t articulate the ethical principles of the things we do and the decisions we make very well. And we need to develop that language so that the ethicist people understand that we don’t just do this without considering those things

Participant #19

This lack of development of thinking about ethics from the perspective of public health is echoed in the literature. Bayer calls for an “articulation of ethical principles for public health practitioners”. Callahan & Jennings enumerate four types of ethics analysis that need to be developed within public health: 1) professional ethics, 2) applied ethics, 3) advocacy ethics and 4) critical ethics, to which list I would add a fifth i.e., public health research ethics. In order to advance the discussion of public health ethics, they recommend several strategies including: 1) convening conferences and symposia whose primary purpose is to further the discussion, 2) encouraging editors of public health journals to prioritize the publication of public health ethics articles, 3) developing a set of cases for discussion, 4) developing public health research capacity, and 5) facilitating education both of ethicists about public health and of public health scholars about ethics. Small steps have been taken to carry out these recommendations. For instance, PHAC has now sponsored two conferences about public health ethics, the first in Montreal in 2007 (First Canadian Roundtable on Public Health Ethics) and another in 2009 in Ottawa called the ‘Ethical
Issues, Challenges and Opportunities in Public Health Practice and Research’. PHAC has also financed the National Collaborating Centre for Healthy Public Policy, located at the Institut national de santé publique du Québec. It is developing general public health ethics-related resources and has used some material published by scholars at the Joint Centre for Bioethics about pandemic preparedness and ethical issues that might arise during a pandemic or smaller infectious disease outbreaks. It also sponsored a workshop on public health ethics in March 2010. The Alberta Research Ethics Community Consensus Initiative (ARECCI) also sponsored a conference in 2008 to discuss these issues. A new journal called ‘Public Health Ethics’ has been created and the University of Toronto continues to offer a course called ‘Public Health Ethics’ to its students. The Joint Centre for Bioethics has formed a group called Research and Education in Research Ethics (RE) to develop an e-portal about resources available in research ethics and public health research ethics, to develop educational tools and courses about the subject and to promote academic discussion about research ethics. Once these discussions are more mature, and the ethical principles guiding public health developed further, perhaps the practice versus research distinction will matter a little less.

**D2. Incorporate my Insights into Guidance Documents**

The image that I have described of the research ethics review system operating under extreme conditions such as those that occurred during the SARS outbreak may never again be attained. It reveals how cumbersome the research ethics review process is, and must be seen as an opportunity to tackle the systemic problems described above and take the next steps toward solving these problems. CIHR has sponsored a project called ‘to REB or not to REB’, which is trying to develop a workable algorithm to decide whether a project needs to be reviewed by an REB. Alberta Research Ethics Community Consensus Initiative (ARECCI) has an on-line template to decide if a project requires
REB review. The CIHR project could draw both on this resource and on my insights into research ethics review in order to finish this project, test how workable it is, implement it and disseminate the results.

While the revised draft 2nd edition of the TCPS has a new section on public emergencies, and despite the fact that the authors do not want the TCPS to be prescriptive, the section is perhaps short on procedural ideas about how research ethics review might be carried out during a public emergency. I feel that there are important insights presented in my ‘emergency review’ paper (part IV of this thesis) and that it could be drawn upon to further develop the procedural language in this section.

D3. Test ‘Emergency Review’

‘Emergency review’ is designed to be used as a framework to guide the development of specific procedures/protocols for research ethics review during a public emergency in individual REBs. These protocols and procedures should then be implemented with a sample of protocols. However, we should not wait until the next outbreak or pandemic to do this. ‘Emergency review’ could be tested in a regular setting perhaps initially using a small proportion of an REB’s high risk submissions. At first this could be done in parallel with the regular review, with the result that two reviews would then be performed on these protocols. Once the REB is familiar with the process of ‘emergency review’, and satisfied that it produces reviews that are as good or better than the usual review on specified outcomes, it might be expanded to include more protocols. Eventually a comparison of two REBs within the same university system, one using the ‘emergency review’ process and one without using it might occur, especially in the context of multi-site review of the same protocol. Alternately a pre-post scenario or a comparison of several smaller REBs each randomized to ‘emergency review process’ or ‘no emergency review’ might be used. Face-to-face
interviews might also be conducted to get reviewers comments about the ‘emergency review’ process. These comments could then be used to refine and improve the procedures.

In order to evaluate the efficacy of the procedures that were developed for ‘emergency review’, detailed documentation would need to be kept about each review performed in the above studies. This documentation would include the speed of review, the number and expertise of the reviewers and the time that each reviewer spent studying and evaluating the protocol. Some estimate of the risk of each proposal to participants and/or to the community would need to be made. ARECCI has developed a tool which assigns a numeric estimate of level of risk and this tool might be used to evaluate level of risk and thus the level of ‘emergency review’ that is required. Currently there are no validated measures for evaluating REBs; the study might also evaluate whether the proposed outcomes of speed, level of scrutiny, proportionality and the ARECCI tool could be validated. Depth of review would need to be evaluated on a per protocol basis. The number of ethical and scientific issues raised would need to be carefully evaluated. Simply counting their number would not be sufficient, since a reviewer who lacks sufficient expertise may question some aspect of the science, which a more knowledgeable person knows is not a problem. Several practical elements might also be developed concurrently with the testing of ‘emergency review’. These might include a process of e-submissions and the development of videoconferencing capabilities now that they are officially sanctioned for occasional use in Canada.

E. Concluding Remarks

The goal of this thesis was to describe and analyze the outcomes of severe acute respiratory syndrome (SARS) survivors and the ethical issues related to research inquiries conducted during the SARS outbreak. This included an examination of the process of research ethics review and the
formulation of a novel framework for research ethics review during a public emergency. The studies used several methodologies some of which are standard practice in clinical research (e.g., observational studies and chart [or file] review). It also used grounded theory, a method that was developed in the social sciences, and applied it to a biomedical and public health setting in the context of a bioethics thesis. I have described the changes that took place in research ethics review during an outbreak of infectious disease and revealed flaws in the current system of research ethics review. The isolation of researchers, REBs and public health officials was exposed as each operated in their own silo or solitude and did not communicate effectively with each other. Conflict of interest arose during the research ethics review of SARS-related protocols and is a complex problem that may take many years to resolve. The insights developed in this study may help to standardize procedures to be used for ethical review of research proposals during a public emergency and to inform both the further development of the “Institutional Emergency Research Ethics Preparedness Plan” section of the TCPS 16 and the discussion about the restructuring of the governance of the REB system in Canada so that institutional conflict of interest is less likely to occur.
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APPENDIX I

SARS Outcomes Study Consents
(CSRN + Follow-up study)

UHN REB approval
CONSENT FORM

UNIVERSITY HEALTH NETWORK INVESTIGATORS:
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(416)340-4410
Dr. James Brunton
Division of Infectious Diseases
Dr. Jagdish Butany &
Dr. Sylvia Asa
Department of Pathology
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CLINICAL TEAM LEADER:
Dr. Marie Louie
Sunnybrook & Women College HSC
Telephone: (416)480-5367

TITLE: Towards an Understanding of Severe Acute Respiratory Syndrome (SARS): The Canadian SARS Research Network

You are being asked to take part in a research study. Before agreeing to participate in this study, it is important that you read and understand the following explanation of the proposed study procedures. The following information describes the purpose, procedures, benefits, discomforts, risks and precautions associated with this study. It also describes your right to refuse to participate or withdraw from the study at any time. In order to decide whether you wish to participate in this research study, you should understand enough about its risks and benefits to be able to make an informed decision. This is known as the informed consent process. Please ask the study doctor or study staff to explain any words you don’t understand before signing this consent form. Make sure all your questions have been answered to your satisfaction before signing this document.

Background

Severe Acute Respiratory Syndrome (SARS) is a new illness first recognized in Canada in early March 2003. As of April 30, 2003 Health Canada has received reports of 344 probable or suspect cases of SARS. The cause of SARS is thought to be a new type of Coronavirus, which has not previously infected man. Currently there is no validated diagnostic test for SARS...
available in the microbiology lab so the diagnosis is made on the basis of patient history. SARS as an illness usually presents as fever, cough and shortness of breath. Currently there is no proven treatment for SARS. Although most patients will recover from SARS, it is not currently known if there are any long-term effects on health in patients who recover from SARS.

What is the purpose of this study?

The purpose of this study is to broadly determine several aspects of the epidemiological, clinical, diagnostic, pathologic, and immunologic aspects of SARS. More specifically:

1. To understand risk factors, including underlying genetic risks, for the acquisition and spread of SARS from one person to another.
2. To determine the course of disease in patients suffering from SARS and understand risk factors, including underlying genetic risks, which could affect outcome or response to treatment.
3. To determine the best timing and methods to diagnose SARS.
4. To understand the mechanism for the injury of lung and potentially other organs in patients suffering from SARS.
5. To determine the natural immune response of patients suffering from SARS and aid in the development of preventive measures such as vaccines.

What is required of me during the study?

You have been asked to participate in this study in order to address the above objectives. We have divided this study into three components that will allow us to address these objectives:

a) Diagnostic component of the study
   - this component of the study is designed to investigate the best specimens, timing, and laboratory assays that can be used to diagnose SARS. The investigators would like to study specimens that have been taken from you as part of the work-up of SARS such as blood and/or tissue and would like to collect more specimens (details below) in order to help understand the best specimen, timing, and laboratory assay to use to diagnose SARS.

b) Immunologic component of the study
   - this component of the study is designed to investigate the body’s immune response to SARS (the way the body fights and clears the body of SARS). The investigators would like to study specimens that have been taken from you as part of the work-up of SARS such as blood and/or tissue and would like to collect more specimens (details below) in order to help understand the immune response to SARS and aid in the development of vaccines.
c) Genetic component of the study

- this component of the study is designed to investigate underlying genetic predisposing factors that may put some people at higher risk of acquiring SARS or at higher risk of having a more severe form of SARS. The investigators would like to take a small amount of blood (details below) in order to help understand whether or not there are underlying genetic risk factors that put some people at higher risk of acquiring SARS or spreading SARS or having a more severe form of SARS.

Routine blood that would be drawn as part of your regular care will be taken (Blood work which we recommend to be drawn will be provided to your physicians who will follow these suggestions at their discretion). Four swabs (from your nose, nasopharynx, throat, and rectum) and a sample of urine will be taken at the 3 month follow-up visit to help develop diagnostic tests for SARS, to help find out how long you may carry the virus, and to find out how your body reacts to SARS.

As part of the study you will be asked to follow-up with your physician and/or a study nurse at 3 months, 6 months, and 12 months after you have recovered from SARS. The last three follow-up visits will take approximately an hour to an hour and a half. At each of these visits, you will be asked about any symptoms of SARS and you will be examined for any signs of SARS. At the 3 month follow-up visit, 7tablespoons of blood will be drawn, and at the 6 and 12 month follow-up visits, 4 tablespoons of blood will be drawn at each visit to look for evidence of ongoing SARS infection and to look to see how your body has responded to SARS. And during the last three follow-up visits, standardized questionnaires will be completed.

In addition, if you decide to participate in this study, if any blood samples were taken and stored while you were sick before you entered this study, we are asking for your permission to test these blood samples for evidence of infection with the SARS virus and to look at your immune response to this virus. In addition, if any tissues are taken from you while you are sick from SARS or once you have recovered from SARS (tissues will only be taken if your treating physician requests this as part of your normal care), whether before or after your enrolment in this study, we ask that we can examine these tissues to look at the pathology, genes, proteins, and chemicals released from these tissues in order to look for evidence of disease, evidence of infection with the SARS virus or other infectious agents, evidence of immune response, and evidence of a predisposition for acquiring SARS or for developing a severe form of SARS.

Risks

Version Date: July 8, 2003

A University of Toronto affiliated patient care, teaching and research centre
The risks associated with this study are minimal. The risks involved are limited to those associated with blood draws (commonly associated with bruising and slight discomfort and rarely associated with infection), obtaining nasopharyngeal swabs (associated with slight discomfort), chest x-rays (associated with exposure to a small dose of radiation that is not thought to be of significant risk), and pulmonary function tests (associated with no significant risk). The other drawback of this study is the time commitment involved and you should be aware of this commitment before signing up to participate.

Benefits

You may or may not receive any medical benefit from participating in this study. This study will not interfere in the way patients with SARS are currently treated but is an attempt to find out more about the disease course, diagnosis, and treatment of SARS. Hence the quality of your care will not be affected by this study and there may be no immediate benefits over and above routine care. Information learned from this study may benefit other patients in the future with your disease.

Confidentiality

All blood, tissues, and information obtained during the study will be held in strict confidence and identified with a study number only. The list linking study numbers to patient identifiers will only be available to the site investigators. No names or identifying information will be used in any publication or presentations. No information identifying you will be transferred outside the investigators in this study.

Participation

Your participation in this study is voluntary. Your can choose not to participate or you may withdraw at any time without affecting your medical care.

Compensation

If you become ill or are physically injured as a result of participation in this study, medical treatment will be provided. In no way does signing this consent form waive your legal rights nor does it relieve the investigators, sponsors or involved institutions from their legal and
University Health Network

professional responsibilities.

Questions

If you have any questions about the study, please page the research nurse (__________) at
__________ or Dr. Wayne Gold (416)340-4410. If you have any questions about your rights
as a research subject, please call Dr Ron Heslegrave, Chair University Health Network Research
Ethics Board at (416)948-4438. This person is not involved with the research project in any way
and calling him will not affect your participation in the study.
Consent

I have had the opportunity to discuss this study and my questions have been answered to my satisfaction. I consent to take part in the study with the understanding I may withdraw at any time without affecting my medical care. I have received a signed copy of this consent form. I voluntarily consent to participate in the following aspects of this study:

☐ Diagnostic Testing Component

☐ Immunologic Testing Component

☐ Genetic Testing Component of this Study:
   If you agree to be a part of the genetic testing component of the study, please check which of the following statements is correct:

☐ I agree to supply my blood and/or tissues for genetic testing directly related to SARS research as described for the purposes of this study and also consent to allow my non-identified sample to be used after the conclusion of this study for further SARS research.

☐ I agree to supply my blood and/or tissues for genetic testing directly related to SARS research as described for the purposes of this study but I request that my non-identified samples be destroyed at the end of this study.

Patient’s Name (Please Print) Patient’s Signature Date

I confirm that I have explained the nature and purpose of the study to the subject named above. I have answered all questions.

Name of Person Obtaining Consent Signature Date
Title: Towards an Understanding of Severe Acute Respiratory Syndrome (SARS): The Canadian SARS Research Network - Long-term outcome arm

UHN Investigators: Cathy Tansey (416-340-4800 ext 6945); Dr. Margaret Herridge (416-340-3057); Dr. Wayne Gold (416-340-4410); Dr. Rima Styra (416-340-4825)

Why are we doing this study?

Severe Acute Respiratory Syndrome (SARS) is a new illness that was first recognized in Canada in early March 2003. The cause of SARS is thought to be a new type of virus, which has not previously infected humans. So far, there is no proven test for SARS available so the diagnosis is made on the basis of patient history. There is no proven treatment for SARS. It is also not known if there are any long-term health effects in patients who recover from SARS. The study will determine how quickly your lung function improves, how your ability to exercise returns and how your chest x-ray changes along with your recovery. We will also look back to what happened to you while you were in the hospital and relate those factors to your recovery.

What will happen during this portion of the study?

Follow-up visits to our clinic will be arranged at 3 months, 6 months, and 12 months after you have been discharged from hospital. These three follow-up visits will take approximately 3 to 3½ hours each. At each of these visits, you will be asked about any symptoms of SARS and you will be examined for any signs of SARS by a lung doctor and by an infectious disease doctor. You will be asked to undergo
breathing tests, to walk for 6 minutes and to have a chest x-ray. We would also like you to fill out two(2) quality of life questionnaires each time; the Short Form 36 (5-10 minutes) and the St. George’s Respiratory Questionnaire(5-10 minutes). We are also asking for your permission to review your hospital chart in order to get information about what happened to you while you were in the hospital for SARS. The psychological portion of the study involves completion of several questionnaires that will take 50-60 minutes to complete. You will be sent the questionnaires prior to your visit and it would be helpful if you could bring the completed questionnaires to your follow-up visit. The questionnaires will help us to better understand how you are managing with SARS, to find out about your activities, support and emotional well-being. The research assistant will also ask you some questions either at the time of your visit or over the phone when it is convenient for you. This takes about 10 minutes.

If we have not been able to get the questionnaires to you prior to your visit or you have not been able to complete the questionnaires, the research assistant will provide the forms in the clinic and there might be some time in the clinic to complete them. If you are unable to complete the forms while you are here, you will have the option to return them by courier which will be paid for by the study.

**How will this study help me?**

You will have close medical follow-up in order to see if you have been left with any damage to your lungs or muscles. Drs. Herridge, Gold will give you and your family doctor full access to all information from the tests done. If any lung complications arise that Dr. Herridge can treat in her capacity as a Respiriologist, then she is available to give you this treatment, or if you wish, you may pursue treatment with another physician of your choice.

**How will this study help others?**

The study will help us to understand what happens to patients as they get better from SARS. We will
then be able to tell others what to expect once they are discharged from hospital. This study will also help us understand what further research needs to be done.

**Risks**

The chest x-ray is no different than the one that your family doctor might order; it is associated with some radiation exposure, but this is a minimal and is not associated with any long term health risk. The breathing tests do not cause any discomfort or risk.

**Confidentiality**

Your answers will be disguised and your name will not appear. Only the researchers will see your test results and these results will not have your name attached. All data will be kept in a secure location. If you would like, we will send you a copy of the results when the study is finished.

**Can I decide if I want to be in this study?**

Participation in every part of this study is entirely voluntary. If you decide to be in the study, you can still change your mind and stop at any time. If you decide not to be in the study or to stop being in the study, the care that you receive from your doctors and the hospital will not change at all.

**Questions**

If you have any questions about this study, please call Cathy Tansey at (416)340-4800 ext. 6945, Dr. Margaret Herridge at (416)340-3057, Dr. Wayne Gold at (416)340-4410 or Dr. Rima Styra at (416)340-4825. If you have any questions about your rights as a research subject, please call Dr. R. Heslegrave, Chair of the Research Ethics Board - UHN at (416)946-2163. This person is not involved with the research project in any way and calling him will not affect your participation in the study.
Towards an Understanding of Severe Acute Respiratory Syndrome (SARS): The Canadian SARS Research Network - Long-term outcome arm

CONSENT

The study has been explained to me.
All my questions have been answered.
I have been told that I can refuse to be in the study, and that if I agree to be in the study, I can stop being in the study at any time.
If I refuse to be in the study or decide to stop being in the study, it will not affect my care in any way.
I know that I can ask questions anytime about the study.
I know that my answers will be kept confidential.
No information about me personally will be released without my permission.
I understand that I will receive a copy of this information/consent form.

I agree to be part of the study.

__________________________________________  ________________________________________
Name of Patient (please print)  Signature of Patient

__________________________________________  ________________________________________
Name of person who obtained consent (please print)  Signature of person who obtained consent

__________________________________________
Date and Time

July 7, 2003
Date: October 18, 2005

To: Dr. Margaret Herridge  
Toronto General Hospital  
NCSB 11C-1185

Re: 03-0310-AE  
Towards an Understanding of Severe Acute Respiratory Syndrome (SARS): The Canadian SARS Research Network

REB Review Type: Expedited
REB Initial Approval Date: May 12, 2003
REB Expiry Date: May 12, 2006
Lapse in REB Approval: From May 12, 2005 to October 16, 2005  
Reactivated October 17, 2005

Consent Form(s) Currently Approved for Use: Dated October 7, 2005

The above-named study has received continued approval from the University Health Network Research Ethics Board until the expiry date noted above. If the study is expected to continue beyond the expiry date, you are responsible for ensuring the study receives re-approval. The REB must also be notified of the completion or termination of this study and a final report provided. In the future please submit the annual renewal form before the REB expiry date to avoid a lapse in REB approval.

If, during the course of the research, there are any serious adverse events, changes in the approved protocol or consent form or any new information that must be considered with respect to the study, these should be brought to the immediate attention of the Board. As the Principal Investigator, you are responsible for the ethical conduct of this study.


Sincerely,

Ronald Heslegrave, Ph.D.  
Chair, University Health Network Research Ethics Board

RH/mp
APPENDIX II

University of Toronto REB approval
Qualitative Study

Invitation to participate in study

Consent form
Dear Dr. Herridge and Ms. Tansey:

Re: Your research protocol entitled, “Challenges of Conducting Research during an Emergency: Lessons from SARS” by Dr. M. Herridge (supervisor), Ms C Tansey (PhD candidate)

ETHICS APPROVAL

<table>
<thead>
<tr>
<th>Original Approval Date: November 9, 2006</th>
</tr>
</thead>
<tbody>
<tr>
<td>Next Expiry Date: November 8, 2011</td>
</tr>
<tr>
<td>Continuing Review Level: 1</td>
</tr>
<tr>
<td>Renewal: 4 of 4</td>
</tr>
</tbody>
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We are writing to advise you that you have been granted annual renewal of ethics approval to the above-referenced research study through the REB’s delegated process. Please note that all protocols involving ongoing data collection or interaction with human participants are subject to re-evaluation after 5 years. Ongoing projects must be renewed prior to the expiry date.

Please note that all protocols involving ongoing data collection or human interaction are subject to full re-evaluation after 5 years. You will be required to submit a new application for review by the appropriate REB if you plan on recruiting participants beyond November 2011. If you are still recruiting by November 2011 and submitting a new application, please refer to "21685 (renewal 4 of 4)" after the title of the research project.

Any changes to the approved protocol or consent materials must be reviewed and approved through the amendment process prior to its implementation. Any adverse or unanticipated events should be reported to the Office of Research Ethics as soon as possible. If your research has funding attached, please contact the relevant Research Funding Officer in Research Services to ensure that your funds are released.

Yours sincerely,

Marianna Richardson
Research Ethics Coordinator
Consent for Participation in a Research Study
Investigator

Study Title: Severe Acute Respiratory Syndrome (SARS): Implications for Research Ethics

Investigator: Cathy Tansey 416-340-4800 ext 6945

You are being asked to take part in a research study. Before agreeing to participate in this study, it is important that you read and understand the following explanation of the proposed study procedures. The following information describes the purpose, procedures, benefits, discomforts, risks and precautions associated with this study. It also describes your right to refuse to participate or withdraw from the study at any time. In order to decide whether you wish to participate in this research study, you should understand enough about its risks and benefits to be able to make an informed decision. This is known as the informed consent process. Make sure all your questions have been answered to your satisfaction before signing this document.

Background: The procedures that were used to approve SARS protocols has not been documented in the literature. The challenges of doing research in an outbreak begin early on. A proposal must be put together on very short notice. Basic ethical premises require that research must be valid, must make good use of scarce resources, and must be feasible. The development of a research protocol usually begins with the discussion of ideas with colleagues, followed by a pilot study to explore feasibility issues. This is not possible in the context of an outbreak. Research results are normally evaluated and integrated into health care practice over years. In the context of an outbreak, this time course is much shorter with projects formulated, carried out and disseminated over weeks or months. How this shorter time-line affected investigators, REB approval and the research protocols that were carried out has not been characterized.

All of those asked to participate in an interview will have had some involvement in conducting or approving research during the SARS outbreak. Discussion will be focussed on areas that were particularly challenging and on what would have helped to make the process less demanding.

Purpose: The objective of the interview is to elicit investigators’ reactions to and ideas about how they dealt with the short time course in formulating and conducting protocols during the SARS outbreak in Toronto. The information gained will help to generate ideas to facilitate timely research during future outbreaks.

Procedure: The study will involve a one-hour interview at a location of your choice. The discussion will be audiotaped for the purpose of transcription and to ensure that I have captured your thoughts and opinions accurately.

Risks: You may find it difficult to relive the trying time during which SARS occurred but please be aware that you may withdraw from the interview at any time, or refuse to answer any question. While every precaution possible will be taken, with the small number of people interviewed, anonymity in such a small research cell cannot be guaranteed. Transcripts will be available only to study team members. In the transcription process all names or other identifying features will be removed. All data will be reported.
anonymously in publications arising from the study. Tapes and transcripts will be kept in a locked cabinet in the principal investigator’s office. Should any of your comments be directly quoted in publication, you will be given the opportunity to review them prior to submission.

**Benefits:** There will be no direct benefit to you as a result of participating in this study, but your participation may help to improve the research process during an outbreak in the future.

**Confidentiality:** All information obtained during the study will be held in strict confidence. You will be identified with a study number only. No names or identifying information will be used in any publication or presentations. Your responses will be stored in a locked filing cabinet.

You should know that the Research Ethics Boards of the University Health Network and the University of Toronto have reviewed this protocol. You do not waive any legal rights by consenting to this interview.

**Compensation for Injury:** There will be no compensation for your participation in this interview. In no way does signing this consent form waive your legal rights nor does it relieve the investigators or involved institutions from their legal and professional responsibilities.

**Participation:** Your participation is VOLUNTARY and you may withdraw from the study at any time, or refuse to answer questions that make you feel uncomfortable.

**Questions:** If you have any questions about the study, please call the investigator Cathy Tansey at (416) 450-4800 ext 6945. If you have any questions about your rights as a research participant, please call Chair of the Research Ethics Board

**Consent:**

I have had the opportunity to read the information about this study and my questions have been answered to my satisfaction. I consent to take part in the study with the understanding that I may withdraw at any time or may refuse to respond to any question that I feel uncomfortable with. I have received a signed copy of this consent form. I voluntarily consent to participate in this study.

☐ I agree to allow the research team to review the correspondence and notes that pertain to my application to the Research Ethics Board for my SARS-related work.

Participant’s Name (Please Print)                Participant’s Signature                Date

I confirm that I have explained the nature and purpose of the study to the participant named above. I have answered all questions.

Name of person obtaining consent                Signature                Date

version September 12, 2006
Consent for Participation in a Research Study

REB member

Study Title: Severe Acute Respiratory Syndrome (SARS): Implications for Research Ethics

Principal Investigator:    Study Team:
Cathy Tansey 416-340-4800 ext 6945    Dr. Margaret Herridge 416-340-3057
                                  Dr. Jim Lavery 416-673-6568
                                  Dr. Ron Heslegrave 416-340-4557

You are being asked to take part in a research study. Before agreeing to participate in this study, it is important that you read and understand the following explanation of the proposed study procedures. The following information describes the purpose, procedures, benefits, discomforts, risks and precautions associated with this study. It also describes your right to refuse to participate or withdraw from the study at any time. In order to decide whether you wish to participate in this research study, you should understand enough about its risks and benefits to be able to make an informed decision. This is known as the informed consent process. Make sure all your questions have been answered to your satisfaction before signing this document.

Background: The procedures that were used to approve SARS protocols has not been documented in the literature. The challenges of doing research in an outbreak begin early on. A proposal must be put together on very short notice. Basic ethical premises require that research must be valid, must make good use of scarce resources, and must be feasible. The development of a research protocol usually begins with the discussion of ideas with colleagues, followed by a pilot study to explore feasibility issues. This is not possible in the context of an outbreak. Research results are normally evaluated and integrated into health care practice over years. In the context of an outbreak, this time course is much shorter with projects formulated, carried out and disseminated over weeks or months. How this shorter time-line affected investigators, REB approval and the research protocols that were carried out has not been characterized.

All of those asked to participate in an interview will have had some involvement in conducting or approving research during the SARS outbreak. Discussion will be focussed on areas that were particularly challenging and on what would have helped to make the process less demanding.

Purpose: The objective of the interview is to elicit REB members’ reactions to and ideas about the changes in the REB process that took place during the SARS outbreak in Toronto. The information gained will help to generate ideas for improving the investigative and REB processes during future outbreaks.
Procedure: The study will involve a one-hour interview at a location of your choice. The discussion will be audi-taped for the purpose of transcription and to ensure we have captured your thoughts and opinions accurately.

Risks: You may find it difficult to relive the trying time during which SARS occurred but please be aware that you may withdraw from the interview at any time, or refuse to answer any question. While every precaution possible will be taken, with the small number of people interviewed, anonymity in such a small research cell cannot be guaranteed. Transcripts will be available only to study team members. In the transcription process all names or other identifying features will be removed. All data will be reported anonymously in publications arising from the study. Tapes and transcripts will be kept in a locked cabinet in the principal investigator’s office. Should any of your comments be directly quoted in publication, you will be given the opportunity to review them prior to submission. The goal of the study is not to look for ethical violations, since we do not have established policy in Canada. However, should I discover evidence of serious wrong-doings either of a legal or ethical nature, I would bring this evidence to the attention of my thesis advisory committee to determine the appropriate actions.

Benefits: There will be no direct benefit to you as a result of participating in this study, but your participation may help to improve the research process during an outbreak in the future.

Confidentiality: All information obtained during the study will be held in strict confidence. You will be identified with a study number only. No names or identifying information will be used in any publication or presentations. Access to audio tapes and other study materials is restricted to the members of the study team, listed at the top of the first page of this information sheet. Audio tapes and other identifiable information will be kept for 6 years in a locked filing cabinet in the office of the principal investigator and destroyed after that time under the supervision of the principal investigator.

You should know that the Research Ethics Boards of the University Health Network and the University of Toronto have reviewed this protocol. You do not waive any legal rights by consenting to this interview.

Compensation for Injury: There will be no compensation for your participation in this interview. In no way does signing this consent form waive your legal rights nor does it relieve the investigators or involved institutions from their legal and professional responsibilities.

Participation: Your participation is VOLUNTARY and you may withdraw from the study at any time, or refuse to answer questions that make you feel uncomfortable.

Questions: If you have any questions about the study, please call the investigator Cathy Tansey at (416) 450-4800 ext 6945. If you have any questions about your rights as a research participant, please call, Chair of the Research Ethics Board at [phone number removed] You may also contact Jill Parsons at jc.parsons@utoronto.ca or 416-946-5806 at the Ethics Review Office at the University of Toronto.
**Study Title:** Severe Acute Respiratory Syndrome (SARS): Implications for Research Ethics

**Consent:**

I have had the opportunity to read the information about this study and my questions have been answered to my satisfaction. I consent to take part in the study with the understanding that I may withdraw at any time or may refuse to respond to any question that I feel uncomfortable with. I have received a signed copy of this consent form. I voluntarily consent to participate in this study.

☐ I agree to allow the research team to review my correspondence and notes in SARS-related submissions.

Participant’s Name (Please Print)  Participant’s Signature  Date

I confirm that I have explained the nature and purpose of the study to the participant named above. I have answered all questions.

Name of person obtaining consent  Signature  Date

version November 1, 2006
January 10, 2006

Re: Challenges of conducting research during the SARS outbreak

Dear investigator,

As you are well aware, many restrictions were in effect in hospitals during the months while SARS was present in our city. During that time, you submitted a research protocol to the Research Ethics Board to investigate some aspect of the SARS virus and/or its effects. In the context of an outbreak, the preparation and implementation time for a research protocol is much shorter than usual with projects formulated, carried out and disseminated over weeks or months. How this shorter time-line affected investigators, REB approval and the SARS-related research protocols that were carried out has not been characterized.

In order to understand some of the complexities involved in conducting research under outbreak conditions, Cathy Tansey, a PhD candidate at the Institute of Medical Science and a long time researcher, has submitted a proposal to the REB to interview investigators who worked with SARS-related projects. She is interested in whether designing the proposal, writing up the consent form, getting REB approval and carrying out the project were different from your experience with other research projects. She would like to interview researchers and REB members to get their ideas on what changes, if any, occurred in the research process, what worked well and what might help the research community prepare for the next outbreak.

Interviews are expected to last about 1-1½ hours, and will be carried out at a location and time of your choice. Please note that this message is being sent by the REB on behalf of the researcher to protect your identity. Should you wish to do so, you may contact the REB about this letter at [phone number]. If you wish to participate in this study, please contact the researcher directly at:

catherine.tansey@utoronto.ca
extension 14-6945 at inside hospital
(340-4800 ext 6945 from outside the hospital)

On behalf of Cathy Tansey PhD candidate, the REB would like to thank you.

Thank you
APPENDIX III

Data collection form (REB survey)

Interview Guides
Evaluation of Research Ethics Board Submissions during the SARS Epidemic
DATA COLLECTION FORM
SARS Protocols

Site: _____________________________

Submission Information

Title: _______________________________________________________________________

Investigators & sub-specialty(with email addresses):__________________________________
__________________________________________________________________________
__________________________________________________________________________
__________________________________________________________________________

Date of Submission:      ________________________
Month(written out) day year

Study design: Clinical - Observational Interventional (more details on rear as needed)
(circle all that apply)
Observational       Interventional       (more details on rear as needed)
Microbiological     Diagnostic       Genetic       Immunological

Primary outcome: _______________________________________________________________
Criteria for premature withdrawal from study:_________________________________________
_____________________________________________________________________________

number of proposed patients: ______           number of proposed visits/patient_______________
approximate size of eligible population from institution/practice:__________________________
inclusion/exclusion criteria: _______________________________________________________
_____________________________________________________________________________
_____________________________________________________________________________
incremental risks above usual care:_________________________________________________
type of data analysis proposed:____________________________________________________

method of patient contact: mail in survey   telephone   face-to-face meetings   specimen
draw
who will make initial contact:____________________ who will obtain consent:______________

Consent obtained:   yes   no
Evaluation of Research Ethics Board Submissions during the SARS Epidemic

DATA COLLECTION FORM

SARS Protocols

REB information

number of people (and their expertise) who reviewed the proposal: _______________________

approval type: (circle) expedited regular
approved via: (circle) face-to-face meeting email/phone

revisions requested: yes no (record details as needed)

date of approval/rejection (circle): Month(written out) day year

number of sites that proposal was submitted to (list):

1) ________________________________________________________

2) ________________________________________________________

3) ________________________________________________________
REB member Interview Guide

Potential Interview questions:

1. About the protocols:
   Did you feel that the protocols submitted were as well thought through as usual?
   Did you have any sense of how many SARS protocols were submitted?
   Were there more questions than usual from researchers before submission?
   Did more investigators than usual mention a tight time frame?
   Were any of the procedures scheduled to be used in the protocols different than usual because of quarantine? Eg-special filters needed or was extra time needed between patients for gowing or for thorough cleaning?

2. About patient rights:
   Were there any special issues that came up as you reviewed these protocols? Or any issues that were different that usual because of the outbreak?
   Did the protocols talk about the possibility of healthcare workers in the protocols?
   Do you think that healthcare workers need special protection when they are patients in their own institution?
   Did you have any sense of multiple protocols competing for a small pool of patients?

3. About consents:
   Was the quality of consent forms put forth during SARS different than those that you usually review? better? worse?
   How did research groups address the lack of knowledge about this outbreak?

4. About the process:
   Were you allowed into your regular workplace?
   Was the regular flow of your work disrupted?
   Were more meetings than usual scheduled?
   What happened when staff was not allowed to meet?
   Does the REB have equipment for video-conferences? Or someone on staff with the knowledge of how to set them up? Were IT people around to help?

5. About future outbreaks:
   Based on your experience with the reviews that you were involved in, was there something that you would like to have seen done differently?
   Was there any protocol that was particularly challenging to review, because the ethical issues were impacted differently than usual?
Investigator Interview Guide

**Potential Interview questions:**

1. About type of studies usually conducted:
   - What type of research do you conduct? Basic science? Observational? Interventional?
   - Was your study conducted during the time when there were restrictions on meetings?

2. About protocol writing:
   - How long did it take you to write up you protocol?
   - Did this include the thinking time?
   - How different is this from your usual protocol writing pattern?
   - Was it a group effort?
   - Did you need to recruit any new expertise to your group?
   - Is this how your group normally generates ideas for research?
   - Was there anything strikingly different in this process because it was SARS?
   - Did you do a power calculation? If yes, where did you get your estimates from?
   - Did you feel a greater time pressure than usual?

3. About consent forms:
   - How difficult did you find writing the consent form?
   - Were the gaps in knowledge about the virus/illness a problem for your protocol?
   - What was your previous experience writing consent forms?
   - Did you use the templates that are on the UNH REB web site? Do you find them helpful?

4. About REB approval:
   - Did you apply for expedited review? Did you get it?
   - Was it a minimal risk protocol?
   - How long did it take to get approval?
   - Was this shorter or longer than what you usually expect?
   - How many other REBs did you submit to?

5. About recruiting patients to the protocol:
   - Where did you recruit your patients from? Is this your usual source?
   - Was there anything special about the patients or the process?
   - Did you have a lot of healthcare workers in you sample? If yes, did you take any special measures because of this?

6. About your working group:
   - Did you expand your working group in any way because of something special about conducting research during SARS?
   - Did you interact at all with public health in your research role? Is this something that you normally do?
7. About funding and infrastructure:
   Where did your funding come from?
   Did you make a special application for these funds?
   Was your infrastructure in place?
   Did you use staff pulled from other projects or did you hire new people?
   Was your work held up by the hospital decision to class research personnel as non-essential?

8. About publication:
   Was authorship discussed before carrying out the project? Is this how your group normally operates?
   Did you have any difficulty getting your work published?
APPENDIX IV

MODEL Evolution
Model 1 - 3 interviews

4 themes identified
- 1) process
- 2) patient
- 3) science
- 4) role of the researcher
Model 1 - 3 interviews

Themes

**Science theme**

- (31) authorship
- (32) leadership
- (33) research funding
- (34) research responsibility
- (35) working groups
- (36) protocol planning
- (37) reaction to fear
- (38) conflict of interest
- (39) importance of
- (311) philosophical underpinning

**Patient theme**

- (21) benefit of being a research subject
- (22) burden of being a research subject
- (23) consequences of illness
- (24) fear
- (25) haven
- (26) loss of opportunity
- (27) research motivation
- (28) stigma
- (29) isolation from family
- (31) community consent

**Role of researcher theme**

- (41) appreciation of relationships
- (42) interviewee's perspective
- (43) appreciation of relationships
- (44) obligation to research subjects
- (45) past experience
- (46) reaction to fear
- (47) recruitment
- (48) role of researcher
- (49) subject retention
- (411) emotional response
- (410) protocol planning

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**Themes:**

- (20) patients
- (21) benefit of being a research subject
- (22) burden of being a research subject
- (23) consequences of illness
- (24) fear
- (25) haven
- (26) loss of opportunity
- (27) research motivation
- (28) stigma
- (29) isolation from family
- (31) community consent
- (32) leadership
- (33) research funding
- (34) research responsibility
- (35) working groups
- (36) protocol planning
- (37) reaction to fear
- (38) conflict of interest
- (39) importance of
- (311) philosophical underpinning
- (41) appreciation of relationships
- (42) interviewee's perspective
- (43) appreciation of relationships
- (44) obligation to research subjects
- (45) past experience
- (46) reaction to fear
- (47) recruitment
- (48) role of researcher
- (49) subject retention
- (411) emotional response
- (410) protocol planning

---

**Model 1 - 3 interviews**

**Themes**

- (20) patients
- (21) benefit of being a research subject
- (22) burden of being a research subject
- (23) consequences of illness
- (24) fear
- (25) haven
- (26) loss of opportunity
- (27) research motivation
- (28) stigma
- (29) isolation from family
- (31) community consent
- (32) leadership
- (33) research funding
- (34) research responsibility
- (35) working groups
- (36) protocol planning
- (37) reaction to fear
- (38) conflict of interest
- (39) importance of
- (311) philosophical underpinning
- (41) appreciation of relationships
- (42) interviewee's perspective
- (43) appreciation of relationships
- (44) obligation to research subjects
- (45) past experience
- (46) reaction to fear
- (47) recruitment
- (48) role of researcher
- (49) subject retention
- (411) emotional response
- (410) protocol planning
Model 2 - 6 interviews

REB theme

- TCPS
- guides
- isolation
- dilemma
- reinterpretation of rules
- some protocols rejected
- may lead to
- political impedance
- may lead to
- hospital administration

- time pressure

- Public Health
- Questions about research/surveillance distinction
- may impede

protocol

Role of researcher theme

- protection of privacy
- barriers to recruitment
- loss of opportunity for patients

- quarantine
- stigma
- production of new knowledge
- lack of leadership
- opportunism
- isolation

need for systematic central process for tracking cases
questions about research/outbreak investigation distinction

Infection control measures may impede loss of opportunity for patients

TCPS guides

REB

dilemma reinterpretation of rules

may impede

hospital administration

Questions about research/outbreak investigation distinction

Infection control measures

protocol

Who decides what is research?

Academics in consultation with public health

may impose measures

may not agree Individual REBs

Feeling like an 'outsider'

Protection of staff 'subjects'

Reluctance to approve protocols that could be either research or outbreak investigation

Infection control measures

production of new knowledge

leadership

need for diagnostic test

researchers mentioned need for systematic central process for tracking cases

time pressure

protection of privacy

barriers to recruitment

loss of opportunity for patients

time pressure

researchers mentioned need for systematic central process for tracking cases

Model 3 - 9 interviews
Many SARS protocols submitted and researchers requesting rapid turn-around

*my interpretation of what REB members told me together with what I saw in the REB survey
During SARS
↑ phone contact
↑ e-mail correspondence
communication not just through the protocol

Model 4 con’t

REB

protocol

Researcher

REB

REB

REB

REB

REB
REB adaptations

Model 5 - 19 interviews

TCPS
- guides

Infection control
- impeded

Questions about research/surveillance
- perplexed

Hospital administration
- may interfere

REB
- time pressure

Sped up turn-around time

Changed prioritization of protocols

Re-interpreted membership rules

Consulted outside expertise

Modified communication strategies
Protocol adaptations

- Protocol planning happened very quickly
- REB submission was easy when single site involved; very challenging if project was multi-site - suggestion was made for a central REB
- Consent ing required adaptations e.g. using internet/phone-in consents for surveys instead of paper
- Recruitment - difficult to identify target population when there is no diagnostic test - and public health is the repository of the contact information - need for systematic central process for tracking cases
- Subjects - health care workers as patients/participants made projects challenging
- Work space - Infection control measures required adaptations of working space e.g. working at home with confidential data; meeting patients in the parking lot; research personnel not entering more than 1 hospital

Model 5 - 19 interviews

time pressure
Model 6 - 19 interviews

Stressors felt by REBs
- Infection control measures
- Public Health surveillance/outbreak control - what is research?
- Pressure exerted by hospital & provincial authorities to approve protocols

Interfered with normal functioning

REB-Researcher Interaction changed

Unused to dealing with each other

Outbreak
- Changed normal practices

Public Health-Researcher interaction
- Competed for information
- Research funding mechanism disadvantaged researchers working with public health

Responses by researchers
- Research priority became SARS-related
- Protocols were quickly written
- Consent process modified
- Place of research activities changed

Communications became more interactive
- Single-site REB approval was easy
- Multi-site REB approval very challenging
- Multi-centre review suggested

Responses by REBs to the stressors
- Sped up turn-around time
- Changed prioritization of protocols
- Re-interpreted membership rules
- Consulted outside expertise
- Modified communication strategies

REBs

Researchers

Public health

Single-site REB approval was easy
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Multi-centre review suggested