

# CANADIAN LONGITUDINAL STUDY ON AGING (CLSA)

## PROTOCOL

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## SECTION 1: INTRODUCTION

### 1.1. Rationale for the Canadian Longitudinal Study on Aging (CLSA)

Up until very recently, most research on aging has been designed to respond to one specific aspect of aging, such as the identification of risk factors for disease or estimation of the incidence (or the prevalence) of late life diseases. Many studies are cross-sectional, examining seniors at one point in time and even for those studies that are longitudinal; a group of seniors is assembled at baseline and followed over a relatively short period. Cross sectional studies and longitudinal studies with short follow up are of limited value if the goal is to understand the dynamic nature of aging. Cross-sectional designs preclude appropriate examination of the determinants of outcomes and, for those who have a condition of interest, include primarily those who have had the condition for some time resulting in findings that are subject to bias.<sup>(1)</sup> Longitudinal studies of fixed cohorts over time result in a decreasing sample as study participants age, are lost to follow-up or die. This is particularly problematic when individuals who enter the study are already in their senior years. For example, in the Canadian Study of Health and Aging (CSHA) enrolment that was restricted to individuals over the age of 65 years resulted in there being no study participants less than 70 years of age at the second phase of the study (CSHA-2) and none under the age of 75 at CSHA-3.<sup>(2)</sup> As a result, important questions such as, “what factors are associated with the development and progression of cognitive impairment at mid-life?” could not be answered. Furthermore, the sampling strategy that included over sampling in the oldest age groups resulted in high attrition due to death during the study period. Building upon both the strengths and the limitations of previous studies of aging, the CLSA is examining the aging process from mid-life to old age to mitigate some of the challenges highlighted above. The additional advantage of including individuals with an age range that spans mid-life to old age in a longitudinal study is that researchers can study the cumulative effect of factors on the health and well-being of the aging population.

Longitudinal studies that consider aging as a multidimensional phenomenon are relatively recent undertakings and, yet, our ability to capitalize on their findings has been limited. In early studies, investigators recognized the importance of following the same individuals over time to capture the precursors of multiple late life events prospectively. Advances have been made in describing the pathways individuals follow to disease, institutionalization, and death; however, emphasis was placed on understanding aging among the aged. These studies typically enrolled and followed individuals over the age of 65 years (e.g., Bonn Longitudinal Study on Aging, Baltimore Longitudinal Study on Aging). While these important initiatives laid the groundwork for the study of aging by formulating the right questions, in light of the multidimensional nature of aging and attrition through death, had limited power to answer those questions.

Although the body of research on the aged is growing, there is an urgent need for studies that examine the process of aging using adult development and life-course perspectives.<sup>(3;4)</sup> In the adult development and life-course literatures, the concept of life pathways plays an important role in accordance with the sequence, impact and cumulative influences of life events on a range of outcomes. The outcomes include successful aging and transitions into, and out of, critical and sensitive periods related to the aging process (e.g., changes in family structure and changes in work and retirement).<sup>(5-7)</sup> Research on the development of life pathways suggests that individual and contextual factors broaden, deepen and become increasingly differentiated over time.<sup>(8;9)</sup> Age-dependent patterns of changing intrinsic (biological) and extrinsic (environmental) factors are most powerful at times of transitions between life phases.<sup>(6;9;10)</sup> As individuals move along life pathways, they may modify their roles, personal ties



and/or social relationships to meet the demands of their changing physical, psychological, social and biological environments, and employ novel strategies and/or technologies to respond to these changes.

Investigators in many countries now recognize the importance of collecting longitudinal data for understanding aging and informing decision making and this recognition is reflected in studies such as the Health and Retirement Survey, Midlife in the United States (MIDUS), the English Longitudinal Study on Aging (ELSA) and the Survey of Health, Ageing and Retirement in Europe (SHARE). Nevertheless, most of these studies are at best moderately powered to examine interactions between intrinsic and extrinsic factors that are associated with health outcomes. In our review of the literature, we found more than 70 studies with a longitudinal design that concentrated on an older population. Not surprisingly, there has been a move towards increased complexity in sampling, study design, and content. It is beyond the scope of this proposal to review these studies in detail; however, a table summarizing the design and content of the studies is provided in Appendix A.

Our ability to study aging in all its complexity has increased with biological and technological advances, such as the sequencing of the human genome. This, in turn, has led to a call for designing multidisciplinary, longitudinal studies of aging. Several factors make these more complex studies different from their predecessors. The major difference is the ability to study biological (especially genetics), physical, lifestyle, and psychosocial factors in the same individuals, in combination with large sample sizes, resulting in sufficient statistical power to address complex interrelationships and rare outcomes and events. With the emergence of multi-level analytical techniques, we also have the means to study the influence of contextual level factors as well as individual level factors. Thus in the modern era of longitudinal research, we are able to move beyond merely describing change over time to actually studying the dynamic determinants of change within and between individuals over time.

To understand the complex dynamics of the physical aspects of aging and the occurrence of age-related disease, emerging large scale longitudinal studies need to consider that physical functioning involves the complex integration of systems within the body and encompasses both age-related changes and the influence of pathology.(11;12) Physical health needs are significantly associated in a complex manner with gender and showing notable differences between men and women(13); diseases and injuries have been shown to be associated with anxiety, depression(14), disturbances of neuroendocrine and hemodynamic function(15), and apolipoprotein E levels(16), and more generally to physical functioning(17;18) and with decline in disability and well-being.(19) The relationship between risk factors, such as pain, and functional limitations has also been shown to differ across the age spectrum.(20)

Further, our ability to maintain autonomy, engage in society, and perform everyday activities is strongly dependent on our level of psychological functioning and this dependence is magnified as we age. The inclusion of a major psychological perspective in longitudinal studies is key to increasing the relevance of such studies. Most previous large scale adult development and aging studies in psychology have focused on the development of specific psychological processes, such as memory and intelligence (e.g., Betula Project), or have been conducted in the context of specific disorders, such as dementia (e.g., Cambridge City Over 75 Cohort Study and Canadian Study of Health and Aging) or heart health (e.g., British Regional Heart Survey; Edinburgh Artery Study). Change in cognitive functioning is, however, a component of normal aging and is evident beginning in mid-life. Some higher brain functions (e.g.

speed of information processing) are uniquely sensitive to age-related change, while other abilities appear to be well preserved among healthy older adults (e.g., comprehension of word meaning).

In addition to the “mechanics” of cognitive functioning are the “pragmatics” of cognitive functioning which are largely captured under the rubric of social cognition. Social cognition is how we perceive and interpret our world and is both impacted by, and impacts on, our life experiences. Longitudinal research in social cognition, will enable us to understand lives within their temporal (past, present and future), and shifting sociocultural contexts (e.g., family of origin, social network, socioeconomic climate, unemployment, widowhood and divorce). Advancing age is often associated with losses of complex cognitive skills that underlie everyday competence and appear as a function of normative age-related declines.(21;22) Although research has begun to address everyday competence and its antecedents and consequences, relatively few studies focus on the components and mechanisms of everyday competence.(23)

Several studies have suggested that a greater vulnerability to illness among aging individuals results from a decline of their physical and psychological capacities to face stress.(24-28) Chronic and severe psychological distress symptoms are associated with low treatment compliance among adults and therefore have a potential for aggravating concomitant physical health conditions. Psychological distress symptoms are also associated with an increased use of health services, psychotropic drugs and with suicide.(29) Psychological distress could have an indirect effect on health by leading to the adoption of inappropriate lifestyle habits (e.g., food habits, sleep habits, exercise and social activities) and may also directly influence the physiological homeostasis of individuals through the general adaptation syndrome first described by Selye.(30)

In addition, research is also needed to understand both continuity and change in social functioning over time, and to track the reciprocal and interactive effects of social participation, social networks, social support, paid and unpaid work, and the environment as well as their interrelationships with biological, physical, and psychological functioning of an aging person. An individual’s social networks and social support play an integral role in determining health trajectories over time. Both are related to work history patterns (e.g., the link between having children and labour force participation for women) and are central determinants of living arrangements and the broader environment in which individuals live.(31) However, awareness of current socio-demographic trends has yet to be translated into research that actually tracks the relationship between social networks/supports and health over time. For example, there has been conjecture and debate about whether changes such as higher divorce rates and fewer biological children are positive, negative or benign in their effects on social networks, social support and health, pointing to the need for longitudinal data to fill gaps in our knowledge in of these areas.

Beyond family ties, active engagement of the aging population in society is also an important element of aging well, and we expect to find those individuals who are connected through organizations and community groups to have better networks of support than those without such connections.(32) Data are needed to enable researchers to link the social, biological, physical and psychological functioning of an individual to their level of support and follow it through relationships, family members and the extent to which ties are maintained. At a socio-political level, a key issue related to social networks is how different types of social networks (social organization, communities, individuals) influence labour market outcomes and social well-being of an aging population, as well as their relationships with government and institutions in the development of policy, program and service delivery. Participation in

the labour force plays an important role in social functioning and has an influence on successful aging through diverse mediating factors such as income and wealth, self-esteem and social standing, stress, and occupational exposures. Personal characteristics, the environments in which people live and interact, and their interrelationships influence health and well-being.(33;34) Environments have multiple dimensions: built (e.g., housing and neighbourhood amenities), social (e.g., migration behaviours), as well as geographic or physical (e.g., water quality). Research evidence under the caption of person-environment fit demonstrates that congruence between people and their environment has important implications for satisfaction, performance and well-being.(35;36)

Very few longitudinal studies of aging have collected biomarker, genetic or epigenetic data to elucidate the process of aging, and to study how biological processes interact with physical and psychosocial environments to produce deleterious health outcomes. Conceptually, the events responsible for biological aging (from physiological through molecular) have been debated by proponents of environmental effects ("wear and tear" process of aging) and genetic components ("programmed" aging). In humans, there have been extensive efforts using replicative senescence of cells; research on centenarians; comparisons of young versus old at the organ, cellular, and molecular levels; and the study of premature aging syndromes (e.g. progeria) to help understand the mechanisms leading to aging.(37-42) Genetic factors that influence longevity are thought to be those that control survival processes such as DNA repair and antioxidant defense, mechanisms that are also implicated in disease processes such as cancer. The role of apoptosis, or cell death, as a mechanism to eliminate damaged cells, the role of cellular senescence in suppressing cell division, and the mechanisms of telomere loss provide complex and interweaving links with aging.(43) Such research implicates the polygenic nature of the human aging process(44-46), arguing for an integrated approach to the identification of the underlying mechanisms that might be responsible for disease and aging processes.

While genetic variation undoubtedly contributes to general aging and certain age-related diseases, there are many cases of very closely related individuals with the same genetic markers showing substantial variation in the age of onset of, or severity of, disease.(47) There is also evidence that the incidence of disease varies according to life circumstances, such as living in low social-economic status conditions, which is not easy to reconcile with a simple genetic model for disease. Epigenetics provides an attractive concept for such mediators, as the epigenome has dynamic features that can be altered by both the physical and the social environment, in addition to being strongly affected by nutritional factors. Therefore, the epigenome in theory could change during the life course as part of the normal developmental program and in response to a number of life factors. Epigenetic mechanisms that influence gene expression include DNA methylation and/or changes in chromatin structure.(48) Epigenetic mechanisms are vital in controlling how genes interact with the environment. An increasing body of persuasive evidence supports a role for epigenetic changes in the etiology of aging and its associated disease sequelae.(49) Several studies comparing groups of young and old individuals reported an age-dependent decrease in either bulk levels of methylated cytosines or gene-specific DNA methylation in human tissues, including peripheral blood leukocytes.(50-52) The general theme of these studies was consistent with the hypothesis of the epigenome acting to mediate between internal and external environmental signals during the aging process and the genome. However, the common caveat to all these early studies is that individuals were not tracked over time, and the epigenetic measures only reflected a single point in time.

The ability to correlate these epigenetic measures with a large number of phenotypes, biomarkers, physical and social life circumstances, and disease outcomes in a large longitudinal study like CLSA will create the most comprehensive and insightful framework for understanding the mechanisms by which genome function can be altered during aging.(48;49) Importantly, the parallel measurement of DNA methylation and mRNA expression patterns from the same sample will enable researchers to decipher the functional circuitry between the genome, the epigenome and the environment, specifically as it relates to the regulation by epigenetic mechanisms of transcriptional programs associated with aging.

### **1.2. Policy Significance of the CLSA**

One of the most pressing policy implications of an aging population is health and social care affordability.(53) Conservative forecasts suggest that the proportion of seniors in the Canadian population will reach an unprecedented level in the years to come. Nationally, the proportion of the population aged 65 years or more is projected to increase over the next 20 years to approximately 22% of the Canadian population, or almost 10 million Canadians.(54) Total healthcare expenditures in Canada now exceed \$145 billion, the largest expenditure item in provincial budgets. As the baby-boom generation approaches and enters into retirement, this demographic phenomenon will intensify the challenges that Canada faces in supporting an aging population. Their shifting lifestyle choices make them one of the most compelling demographic segments to study. The challenge for health policy makers is the lack of availability of strong evidence to inform clinical, public health, and social policy decision making that is directed toward preventing morbidity and improving the health of Canada's aging population. The CLSA has been launched at a time when there is a need for data that will provide highly relevant information to help improve health and social care policy in Canada.

Health care policy researchers generally agree that changing demographics are not solely responsible for escalating costs. Based on the experience of British Columbia, Barer, Evans and Hertzman(55) argue that increasing health care utilization among seniors has less to do with the fact that there are more seniors than with the fact that the health care system is doing much more to (and for) them. Dalziel(56) further suggests that it is not the aging of our population that threatens to precipitate a financial crisis in health care, but rather a failure to examine and make appropriate changes to our health care system proactively.

The second large policy concern with an aging population can be described broadly under the rubric of social policy. Social policy concerns range from financing Old Age Security nationally and age-based tax credits provincially, to the conversion of elementary schools into Seniors Centres in older neighbourhoods at the community level and adequate preparation for retirement at the household level.(57;58) Perhaps the most pressing public finance concern is the matter of pension plan sustainability and adequate retirement financing. At the same time as life expectancy continues to increase, Canadians had been retiring earlier and earlier, with the retirement age reaching a low in 1997. Even with the financial recession and the recent increase in the eligibility age for Old Age Security benefits from 65 to 67 years, the median retirement age in 2011 was 63.2 for men and 61.4 for women, compared to 61.3 and 59.9, in 1997

Despite the impact of an aging population on health and social policy, there is little research that can be used to inform clinical or policy decision-making. The need for longitudinal data to inform the decisions to design interventions and policies to improve the health and well-being of today and tomorrow's

seniors is widely recognized by researchers and by the federal, provincial, and territorial governments. Indeed, after reviewing a number of policy issues concerning Canadian population aging, Cheal(59) remarked that there is a pressing need for data development. He calls for explicit longitudinal data to be collected if Canadian policymaking is to be appropriately responsive to complex, emerging issues in an aging population. Explicit longitudinal data to inform policymaking would prevent the problem of acting hastily upon myths or common beliefs about aging. For instance, the end-of-life is commonly thought to be a period during which extensive health and social services utilization occurs; however, emerging research is showing considerable variability in end-of-life care needs and therefore health and social service utilization.(60-62)

## SECTION 2: CONCEPTUAL FRAMEWORK

### 2.1. Models of Aging

In developing a conceptual framework for the CLSA, we have drawn on research from the past two decades. The terms healthy aging(63-66), successful aging(67-74), optimal aging, active aging and productive aging(75;76) have all been used to characterize aging beyond the absence or presence of disease. While each term carries a slightly different connotation, they have much in common and have been used interchangeably by various authors. However, there has also been a considerable debate in the literature about the use of the word successful to describe the aging process. Words such as healthy, productive, active or optimal aging also suffer from similar conceptual difficulties.(77) Despite the controversy surrounding the word successful, the concept of successful aging remains useful for understanding the positive aspects of the aging process.

There is an abundance of models and theories related to successful aging, with two of the most influential being Rowe & Kahn's Model of Successful Aging(71) and Baltes & Baltes Model of Selective Optimization with Compensation.(70) These theories reflect different approaches to the study of aging and are reviewed briefly below to situate our conceptual thinking within the broader literature.

In 1987, Rowe & Kahn(71) published a key paper in the journal *Science* in which they differentiated successful aging from usual aging. The authors argued that not only was it important to separate pathological changes from changes attributable to aging, but that in normal aging, a great deal of unexplained heterogeneity occurs within age groups. They conjectured that the decline that is often associated with usual aging is not a result of the aging process per se, but is rather the result of the accumulation of risk factors over time. Therefore, for most people, decline is not an inevitable result of the aging process but is the consequence of engaging in unhealthy behaviours that negatively affect modifiable risk factors over time. It follows then, from this model, that individuals who engage in healthy behaviours (e.g., diet and exercise), thereby avoiding risk factors (e.g., obesity) for disease and disability, are more likely to age successfully with minimal loss in physiological function.

A decade later, based on their own work with the McArthur Foundation Studies of Successful Aging, Rowe & Kahn published their Model of Successful Aging.(78) According to this model, successful aging is determined according to three criteria: (1) a low probability of disease and disease-related disability (including absence of risk factors for disease and disability), (2) high cognitive and physical functional capacity, and (3) active engagement with life (in particular, interpersonal relations and productive activity). This theory of successful aging heralded a change in thinking about aging; in particular, it challenged the notion of aging as a period of inevitable decline.

The Baltes & Baltes Model of Selective Optimization with Compensation(70), on the other hand, is based on the belief that change is an *inevitable* part of aging, and that successful aging requires the engagement of processes to adapt to the changes in order to meet life goals. Rather than using external outcomes to characterize successful aging, this model gauges successful aging by the degree to which people are able to attain their own goals. Baltes and Baltes propose three main mechanisms by which they posit that people can reach their goals in the face of changing circumstances: selection, optimization, and compensation. Selection refers to avoiding or restricting a particular life domain and entails the readjustment of life goals.(67) Optimization refers to enriching and augmenting reserves and resources and thus the enhancement of functioning and adaptive fitness in selected life domains. Finally,

compensation refers to the use of alternative means to reach the same goal. Thus, through this model, aging is viewed as a lifelong adaptive process.

Despite the popularity of these two models, several authors have identified missing components. For example, Riley(79) argues that these two models focus primarily on the attributes of the individual and ignore the role of structural lag or contextual factors on the process of successful aging and suggests that a comprehensive model of successful aging also needs to consider contextual or structural factors such as social structures, norms, and institutions. Furthermore, Strawbridge and Wallhagen(77) have suggested that one of the main concepts missing from the current models of successful aging is what the aging person themselves have to say about their own experiences of aging.

A few researchers have begun to examine more closely what seniors themselves believe is important to age successfully. Seniors' lay theories of aging recognize that individuals exist within a larger social context and a defined value system. Cultural and social norms dictate the roles of older individuals in their communities and influence attitudes towards aging.(80) Cultural views on aging can differ, which, in turn, has a significant impact on the way in which the elderly view themselves.(81) In one qualitative study, seniors perceived adaptation as essential to successful aging and strongly valued well-being, social functioning and active engagement. There was less emphasis on physical and psycho-cognitive functioning.(69) A second study revealed a similar lay theory in which successful aging was seen to mean "going and doing something meaningful" and required four components: something worthwhile to do, balance between abilities and challenges, appropriate external resources, and individual attitudes.(66) Another qualitative research study of persons aged 65 years and older found that independence is multidimensional and involves a sense of control and autonomy, purpose and the ability to adapt to developments within the self and the environment.(65) In a recent investigation based on a short survey of more than 1,500 survivors enrolled in the Manitoba Follow-up Study of 3,983 World War II Royal Canadian Air Force male aircrew, Tate et al. (2003)(74) reported that most self-reported definitions of successful aging were related to health. The second most frequently reported components were happiness, enjoying life and having a satisfying lifestyle. These studies suggest that sense of control, purpose, meaning, and autonomy, are also key components in the study of successful aging. There has been considerable discussion in the literature of a variety of models, however, there seems to have been relatively little attempt to integrate these models, each of which alone is somewhat incomplete. As Kahn (2003)(82) has recently stated the current models of successful aging should be seen as complementary not contradictory and suggests the integration of these models to create a comprehensive model that will guide future research.

## **2.2. CLSA Framework**

To create a comprehensive framework of successful aging to inform the development of the CLSA we have integrated various perspectives of aging described above by Rowe and Kahn (1987)(78), Baltes and Baltes (1990)(70), Riley (1998)(79) and Strawbridge and Wallhagen (2003)(77) We have based our work on the assumption that aging occurs within the context of life pathways and includes multidimensional constructs that are influenced by biological and psychosocial factors. Our operational definition of successful aging, based on current thinking in the literature, includes not only the physical, psychological and social functioning but also incorporates the concept of biology, adaptation, context and the perception of the aging individual.

In the CLSA conceptual framework, the individual predictors, emphasized in the original Rowe & Kahn model, are depicted as feeding into the four higher-level concepts of the CLSA model: physical functioning, psycho-cognitive functioning, social functioning, and the concept of perceived well-being suggested by Strawbridge and Wallhagen (2003). In the CLSA model, the individual level predictors represent not only factors that are within the individual's control (such as health behaviours) as presented in the Rowe and Kahn model, but also factors that are not always within the individual's control (such as chronic disease). The context level predictors include not only available services but also the general attitude of society towards aging and the aged. Both individual and contextual level predictors influence function and well-being. These factors may be proximal, such as overt disease, or more distal, such as the underlying factors that eventually lead to disease. For example, it has been discussed in the literature that human development and aging processes are genetically programmed, but that the expression of genes may be modified by past and present environmental factors such as nutrition, lifestyle and physical and psychosocial environments.(83)

The influence of the Baltes and Baltes model (70) and the Riley model(84) is reflected in the contextual and the individual adaptation in the CLSA conceptual framework. These adaptations represent the understanding that both individual and societal factors can change over time to enhance or impede the process of aging successfully. In this framework, we posit that individuals continually monitor changes in their physical, psycho-cognitive, and social functioning, as well as their perceived well-being. Positive or negative changes in functioning or perceived well-being signal the potential need to adapt or respond to these changes. Adaptation can occur in many ways and at many different levels. For example, at the cellular level, the body will respond to changes in its ability to regenerate; individuals may adjust to changes in physical abilities (e.g., use eyeglasses to compensate for weakening vision) or cognitive abilities (e.g. make lists to help "jog" memory), and adapt to increased leisure time associated with retirement (e.g., developing a hobby or volunteering). Adaptation also occurs at the contextual level. For example, changes in policies encouraging the provision of home care for terminally ill patients may increase demands on family caregivers requiring adaptation in both work and their personal life. Conversely, policy change, such as proposed changes to allow family caregiver benefits, can facilitate adaptation. Contextual change could include the training and recruitment of health professionals, creating continuing education programs, seniors clubs, and leisure activities of interest to older people and changing negative stereotypic views of aging (ageism). Our framework allows separate changes at each level to be captured over time allowing the representation of individual adaptation preceding contextual adaptation.

### **2.3. Overarching Aim of the CLSA**

The CLSA is a large, national, long-term study of adult development and aging designed to examine health transitions and trajectories with the goal of identifying modifiable factors with the potential to develop interventions to improve the health of populations as they age. The CLSA research team includes experts from across Canada in biology, genetics, clinical research, social sciences, economics, psychology, nutrition, health services, statistics, epidemiology, and population health. Through its large sample, multidisciplinary focus, and longitudinal design the CLSA will provide research opportunity unprecedented in Canada, and indeed, internationally. For the first time, there will be the opportunities to begin to understand the complex interplay between determinants of health and enable research to move beyond a snapshot of the adult Canadian population to observe and understand the disease, disability, and psychosocial processes that accompany aging. The CLSA will be one of the most complete studies of its kind undertaken to date in Canada.



Despite long-standing awareness that the aging process relates to multifaceted changes during an individual's lifetime (from cell, to individual psychological and behavioral factors, to broad social contexts), a clear picture of combined effects has not yet emerged. Complex interactions between changing biological, psychological and social factors can take years to present their effects and it is anticipated that these changing factors will most likely manifest themselves differently among baby boomers, i.e. the seniors of tomorrow.

The overall aim of the CLSA is thus to provide the most accurate picture of the dynamic process of adult development and healthy aging that current methodology allows. We will investigate the interrelationship among intrinsic and extrinsic factors influencing health from mid-life to older age. This will allow us to capture transitions and trajectories of aging, elucidate the concept of successful aging, and identify modifiable factors that could be used to develop interventions to improve the health of today's and tomorrow's senior population. The CLSA will provide infrastructure and build capacity for high quality research on aging in Canada and elsewhere.

Specifically, the research objectives of the CLSA will be accomplished by examining the association between sets of quantitative traits, identified in physical, psychological, and social health domains, and the development of disease and psychosocial consequences. We will examine the relationships among precursors (e.g., gene variants, nutrition, physical environment), changes in quantitative traits (e.g., cognition, inflammatory biomarkers), and the consequences of the changing phenotype on the development or prevention of disease (e.g., dementia or depression), disability (e.g., frailty or physical limitations), and psychosocial outcomes (e.g., emotional distress or social isolation). The use of quantitative traits allows for elucidation of direct or indirect causal associations of precursors to the development and progression of disease, disability, as well as psychosocial processes. An advantage of using quantitative traits in the CLSA is that it substantially increases the power to detect main effects as well as interactions. Here we provide a few examples of research questions that could be addressed with CLSA data:

- What are the determinants of changes in biological, physical, psychological, and social function over time and across ages?
- What is the magnitude of the role of genetic and epigenetic factors in the aging process?
- What factors distinguish individuals who experience healthy or successful aging from those who do not?
- Is decline in cognitive functions (memory, executive function, and psychomotor speed) in mid and later life associated with changes in social participation?
- How do changes in mobility impact upon indicators of physical health including falls and other injuries, fear of falls, frailty, disability, and other physical outcomes, adjusting for other factors?
- Are there identifiable patterns of cognitive functioning in midlife that predict the onset of dementia in later life?
- How do work and family transitions intersect with negative/positive changes in social networks and social support and how do these transitions influence overall health?

### SECTION 3: OVERVIEW OF THE CLSA DESIGN

The CLSA is a Canada-wide study of 50,000 people between the ages of 45 and 85 years at baseline. These persons will be followed for at least 20 years. All 50,000 participants are asked to provide a core set of information on demographic and lifestyle/behaviour measures, social measures, physical/clinical measures, psychological measures, economic measures, health status measures, and health services use. Thirty thousand of the 50,000 (i.e., the *CLSA Comprehensive*) are asked to supplement the core set with in-depth information obtained via physical examinations and biospecimens collection. The remaining 20,000 (i.e., the *CLSA Tracking*) provide the core information set only.

The core information set is collected on all 50,000 people at three-year intervals (waves) via CAPI (computer-assisted personal interviews) (CLSA Comprehensive) done in participants' homes and CATI (computer-assisted telephone interviews) (CLSA Tracking) done over the telephone. Additionally, all 50,000 participants are asked to complete a mid-wave, maintaining contact interview via telephone to collect limited additional information on items such as changes of address. All telephone interviews are conducted from dedicated sites at the University of Victoria, University of Manitoba, Université de Sherbrooke, and Dalhousie University.

For the 30,000 members of the CLSA Comprehensive, the core information set is supplemented by additional face-to-face interview questionnaires about diet, medication use, chronic disease symptoms, and sleep disorders. Furthermore, these participants are asked to visit a local data collection site (DCS) to allow for the conduct of a neuropsychological assessment, and the collection of data on physical function (i.e., grip strength, timed-up-and-go, chair rise, four-metre walk, standing balance), anthropometrics (i.e., height, weight, waist and hip circumference, lean muscle mass), and clinical variables (i.e., blood pressure, heart rate, vision, hearing, lung function, electrocardiogram [ECG]). Participants are assessed for bone density, aortic calcification, and carotid intima-media thickness. Visits to data collection sites occur at three-year intervals, following the completion of the in-home interviews. Data Collection Sites are established in 11 cities across Canada: Victoria, Vancouver, Surrey, Calgary, Winnipeg, Hamilton, Ottawa, Montréal, Sherbrooke, Halifax, and St. John's.

Participants in the CLSA Comprehensive are also asked to consent to the provision of blood and urine samples, which are collected during the data collection site visit. To participate in the CLSA comprehensive, persons have to consent to participate in a home interview and to the physical assessments but have the option to refuse to provide blood and/or urine samples.

All 50,000 participants are asked to provide their health insurance numbers to permit linkage with Medicare claims data held in provincial healthcare databases. Participants who do not wish to provide their health insurance numbers are still allowed to participate in the CLSA.

## SECTION 4: STUDY CONTENT

### 4.1. Overview

The study of aging, unlike the study of one particular disease entity or outcome, is broad and multi-faceted, involving the complex interplay of many factors in the internal and external environments. For the purposes of this protocol, we have organized these factors in terms of key elements of aging, biological functioning, physical functioning, psychological functioning, and social functioning.

In this section, we outline the specific measures selected to collect information on the various aspects of biological, physical, psychological, and social functioning of relevance in the CLSA. Many of these measures are included in the study questionnaires (see Appendices B and C). The complete core questionnaire content for the first wave of the CLSA is collected in baseline questionnaires (in-home and DCS questionnaires for the Comprehensive and the CATI-administered questionnaire for the Tracking) and the upcoming maintaining contact questionnaires (CATI-administered questionnaire for both Comprehensive and Tracking).

### 4.2. Study Content Development Process

At the outset of study planning, we established four working groups to develop specific biological, physical, psychological, and social measures for inclusion in the CLSA. We formed two additional working groups to develop the content for lifestyle and behavioural aspects of the CLSA, and a methodology working group whose responsibility was to develop design and sampling methods for the study. These working groups were comprised of experts from genetics, epigenetics, clinical chemistry, biochemistry, dentistry, rehabilitation sciences, demography, sociology, psychology, economics, behavioural sciences, nutrition, epidemiology, nursing, health services, biostatistics and information sciences, as well as several subspecialties of medicine. Under the direction of a theme leader, each working group developed background material, a rationale for proposed content domains, possible research questions, and a list of tools and measurement instruments for possible inclusion in the CLSA.

The working groups were encouraged to focus on:

- multidisciplinary issues considered critical to the understanding of the aging process
- questions that would require a longitudinal approach to study
- areas that were felt to serve a niche: i.e., were understudied or were not the subject of other ongoing or planned studies of aging in Canada or elsewhere, or for which Canada or Canadian researchers were well situated to answer.

As a second layer of refinement, feasibility and practical issues were assessed:

- Is there a tool available to measure this issue/question?
- How long it will take to administer.
- What are the psychometric properties of the tool?
- Is the measure responsive (sensitive enough to detect change)?
- Is it relevant across the CLSA age groups?
- Is the tool available in both English and French
- Are there unique resources or equipment required?
- Is it necessary to use the full sample to study this question, or is this question best answered as part of the core study or as an ancillary study?

A second phase of study content development and refinement was undertaken by the principal investigative teams, and involved the use of strategies to set priorities for content inclusion, as well as to reduce the number of measures.

### **4.3. Biological Functioning**

The opportunities for research and analysis of biological measures are increasing rapidly because of advances in technology, particularly those related to genetics and the mapping of the human genome. These advances provide an unprecedented opportunity for the CLSA to engage in cutting-edge research that will continue to evolve over the course of the study. Some of the many proposed areas for research using biomeasures include various forms of dementia (e.g., Alzheimer's and Parkinson's), immune function (immunosenescence), metabolism (autoimmunity related to diabetes), cardiovascular impairment (atherosclerosis, phytoestrogens and heart attack risk), reproductive aging (factors in menopause), and cell-replication based dysfunctions of aging.

Blood and urine specimens are being collected from the CLSA Comprehensive participants. Blood is collected in six tube types (no additive, citrate, and heparin, EDTA, ACD, and CPT) to produce nine specimen types (serum, four types of plasma, whole blood, buffy coat, preserved cells, and purified peripheral blood mononuclear cells). In addition, whole blood dried in microwell plates containing filter paper is being collected. All processing takes place in the DCS within two hours of collection from the participant. A total of 42 0.5-mL aliquots will be cryogenically stored in the CLSA central biorepository in Hamilton. Baseline analysis includes a complete blood cell count at the DCS. Further analysis will be done in the CLSA Biorepository and Bioanalysis Centre (BBC) and Genetics and Epigenetics Centre (GEC) as well as in other research and clinical laboratories. Section 7 provides further detail on specimen collection, processing, shipping, storage, tracking, and analysis.

### **4.4. Physical Functioning**

The CLSA examines physical functioning in a broader context than is possible in studies of specific diseases or health conditions. Physical functioning in the CLSA includes injuries, chronic diseases of the brain, and of the circulatory, musculoskeletal, respiratory, and endocrine/metabolic systems, oral health, sleep, pain, vision, hearing, physical impairments, limitations in activities of daily living and participation, disability, and ultimately, healthy aging and well-being.

#### *4.4.1. Physical Function Measures*

The depth of information collected about physical function, and the methods for collecting this information, differ between the CLSA Comprehensive and Tracking (i.e., physical examinations and face-to-face interviews are used in the CLSA Comprehensive and telephone interviews are used in the CLSA Tracking). Nevertheless, the majority of measurement domains, and many of the questionnaire-based measures themselves, overlap for the full complement of 50,000 participants. This permits common analyses on the entire CLSA cohort. Table 4.1 presents the CLSA measures of physical functioning and shows the similarities and differences in modes of measurement between the tracking and comprehensive arms of the CLSA. Unless otherwise specified, the questionnaire content is collected during the baseline interview.

**Table 4.1. CLSA Physical Function Measures**

Measure	CLSA	
	Comprehensive (n=30,000)	Tracking (n=20,000)
Lean Muscle Mass and Body Composition	PE	
Waist and Hip Circumference	PE	
Blood Pressure	PE	
Bone Density	PE	
Aortic Calcification	PE	
Lung Function	PE	
Electrocardiogram (ECG)	PE	
Heart Rate	PE	
Carotid Intima-media Thickness	PE	
Vision	PE/Q	Q
Hearing	PE/Q	Q
Weight and Height	PE	Q
Functional Status	PE	Q
Functional Performance	PE	
Basic Activities of Daily Living	Q	Q
Instrumental Activities of Daily Living	Q	Q
General Health	Q	Q
Life Space Index	Q	
Women's Health	Q	Q
Chronic Conditions	Q <sup>1</sup>	Q
Health Care Utilization	Q <sup>2</sup>	Q <sup>3</sup>
Medication Use	Q <sup>2</sup>	Q <sup>3</sup>
Dietary Supplement Use	Q <sup>2,3</sup>	Q <sup>3</sup>
Oral Health	Q <sup>3</sup>	Q <sup>3</sup>
Injury and Falls	Q	Q
Pain and Discomfort	Q <sup>3</sup>	Q <sup>3</sup>
Sleep	Q	

Q: measured by questionnaire (either telephone or face-to-face administration)

PE: measure by physical examination at the data collection site

<sup>1</sup>The CLSA Comprehensive contains additional questions about chronic disease symptoms

<sup>2</sup>DIN information is recorded directly from prescription medications in the CLSA Comprehensive

<sup>3</sup>Measure included in Maintaining Contact Questionnaire only

#### 4.4.2. Properties of Physical Examination Measurement Instruments

CLSA Comprehensive participants as asked to perform five physical performance tests, i.e., grip strength, timed up-and-go, chair rise, standing balance, and a four-metre walk test. They also undergo anthropometric measurement for waist and hip circumference, weight, and standing and sitting height. Additional assessments measure blood pressure, heart rate, vision, hearing, and lung function, as well as bone density, aortic calcification, lean muscle mass and body composition, and carotid intima-media thickness.

The CLSA data collection sites were designed and are functioning with the specific aim of collecting high quality data using state of the art equipment standardized across the 11 sites. Criteria for the choice of equipment included ease of training and usefulness in high-throughput settings. State of the art equipment was chosen to allow digital data transfer of participant data directly from the equipment to

the CLSA central server by virtual private network (VPN), thereby reducing transcription errors and personnel time. In this section, the specific choice of DCS equipment is presented.

#### *Blood Pressure and Heart Rate*

Blood pressure and heart rate are measured using the BpTRU™ BPM200 Blood Pressure Monitor. The BpTRU™ is an automated, non-invasive blood pressure monitor that has been shown to be reliable, accurate, and easy to use. The monitor automatically performs up to five measurements and displays the average of the last four measurements. BpTRU™ incorporates many safety features and self-diagnostic programs to protect study participants and eliminates faulty readings due to improper inflation and deflation of the cuff. A recent study comparing the BpTRU™ to nurse recorded blood pressure measurements for the management of hypertension found 92% (97/106) agreement between the hypertension nurse specialist and the BpTRU™ (kappa 0.83, 95% CI, 0.72 to 0.94).(85) The investigators concluded that the BpTRU™ offers the accuracy of a trained hypertension nurse observer.

#### *Bone Density, Lean Muscle Mass and Body Composition, Aortic Calcification*

Quantitative traits of interest in relation to musculoskeletal function are bone density and strength. Bone density is measured using the Hologic Discovery A™ Dual energy X-ray Absorptiometry (DXA). DXA scanning has become the most widely used method for measuring bone mineral density (BMD) for several reasons. When compared with radiographic absorptiometry or single energy x-ray absorptiometry, DXA scanning documents more precisely small changes in bone mass and is more flexible since it can be used to examine both the spine and the extremities.(86) In bone density measures, a “T score” is the number of standard deviations above or below the mean for a healthy 30 year old adult of the same sex and ethnicity as the participant. The DXA BMD measurement is the “gold standard” for T score assessment and the standard against which other bone imaging measures are evaluated.(87) A meta-analysis of 11 prospective cohort studies found that for bone density DXA measurements at the femoral neck, the pooled relative risk for hip fractures per decrease of 1 SD in bone density was 2.6 (CI, 2.0-3.5).(88) Quantitative Computed Tomography (QCT) is the only other technique that can directly measure bone density and volume. Compared to QCT, DXA scanning is less expensive, exposes the participant to less radiation, and is more sensitive and accurate at measuring subtle changes in bone density over time.(89) Because of the age range of our participants, we have selected an innovative rotational arm technology which allows the participant to remain in a stationary supine position, increasing their comfort and the efficiency of the procedure. In addition to whole body bone density, DXA measures dual hip and forearm bone density, as well as intervertebral assessment of the lateral spine.

DXA is also used to measure lean muscle mass and body composition. A study assessing the validity and reliability of DXA for the assessment of abdominal adiposity found good concordance between DXA and computed tomography for abdominal total tissue mass (i.e., Bland Altman limits of agreement(90) = -1.56 to 2.54 kg) and fat mass (i.e., Bland and Altman limits of agreement=0.40 to 1.94 kg).(91) DXA also showed excellent reliability among three different operators to determine total, fat, and lean body mass in the L1–L4 (abdominal soft tissue composition, defined as the vertebral L1–L4 operator-defined region of interest) (intraclass correlations,  $r = 0.94, 0.97, \text{ and } 0.89$  respectively).(91)

The Hologic Discovery A™ DXA system has recently received U.S. Food and Drug Administration (FDA) clearance to visualize abdominal aortic calcifications, which have been shown to be strong

predictors of coronary heart disease, stroke, and other forms of cardiovascular disease. DXA is also used to measure aortic calcification in CLSA participants.

#### *Lung Function*

The Easy on-PC spirometer was chosen to measure lung function based on the following criteria: met American Thoracic Society (ATS) requirements, easy to use, and data downloadable to the CLSA central server.

#### *Carotid Intima-Media Thickness*

The GE VIVID i® Carotid Doppler Ultrasound measures Carotid intima-media thickness (c-IMT), arterial stiffness, and plaque volume, which are primary quantitative traits of circulatory function and useful to predict individual cardiovascular risk. Ultrasonography is commonly accepted as a non-invasive, safe, inexpensive, and reliable method of measuring the intimal medial thickness of large arteries located close to the skin, such as the carotid and femoral arteries.(92) The GE VIVID i® measurement for intima-media wall is not operator dependent, is simple to use, and takes fewer than four steps to perform. The system generates immediate results for electronic storage and transfer. The sensitivity of the GE VIVID i® for the diagnosis of 70% carotid artery stenosis to near obstruction ranges between 87.0% and 98.6% and the specificity ranges between 59.2% and 75.7%.(93)

#### *Electrical Activity of the Heart*

The MAC 1600 12-lead ECG measures the heart's electrical activity. This instrument is a PC-based cardio-respiratory system. The ECG image and quantitative results are directly transmitted to the CLSA central server. ECG results can be used to assess heart rhythm, blood flow to the heart muscle, and abnormalities of the heart (e.g., heart chamber enlargement, abnormal electrical conduction).

#### *Hearing*

Hearing sensitivity is assessed using the Tremetrics RA 300+ Digital Screening Audiometer. This audiometer requires minimal training to use and can store multiple test results for download directly to the CLSA central server. This audiometer can be reliably used in a quiet room with audio cup headphones to minimize ambient noise. Soundproof rooms are unnecessary. One study that examined tone audiometer (PTA) screening at 40 dB HL from 500 to 4000 Hz in reference to a pure-tone threshold (PTT) test on 20 to 96 year olds found that the PTA screenings were equally accurate in reference to the PTT test.(94) Averaged over the screening tests, the sensitivity was 91.4%, with a specificity of 93.5%.(94) Other longitudinal studies, including the Women's Health and Aging Study (WHAS), have used sound-generating otoscopes to test for hearing sensitivity and to examine the tympanic membrane. However, a sound-generating otoscope is less reliable than an audiometer and the results from an otoscope cannot be directly downloaded to a computer.(95)

#### *Vision*

Visual acuity is measured using an illuminated Early Treatment Diabetic Retinopathy Study (ETDRS) chart. ETDRS vision charts have become the worldwide standard for visual acuity testing.(96) The charts measure acuity using logarithmic scaling of the distance between letters on successive lines, logarithmic progression of lines, and the same number of letters on each line of the chart.

The fluid pressure in the eye (intraocular pressure [IOP]) is measured using the Ocular Response Analyzer®. IOP is an important aspect in the evaluation of glaucoma. We are also employing the device

to obtain corneal compensated IOP, corneal hysteresis, corneal resistance factor, and Goldmann-corrected IOP.

Retinal status is being measured using the TRC-NW8 non-mydratic retinal camera, which does not require pharmaceutical dilation of the pupil. This camera achieves high-resolution images of the interior of the eye, which have been used to detect ocular conditions such as diabetic retinopathy or macular degeneration in other large population-based cohort studies, e.g., National Health and Nutrition Examination Survey (NHANES).(97;98)

### *Functional Performance*

#### Hand Grip Strength

Hand grip strength is used as a measure of 'overall strength' in many aging studies and has been shown to be a good predictor of physical functioning and disability, morbidity, and mortality.(99) Hand grip strength is an estimate of isometric strength in the upper extremity and correlates with strength in other muscle groups.(99) In a Danish study of 8,342 persons aged 45 to 102 years, hand grip strength was found to linearly decrease in the 50- to 85-year age group, with mean annual grip strength losses of 0.59 kg for men and 0.31 kg for women.(99)

Dominant handgrip strengths are measured in the CLSA (unless contraindicated) using the Tracker Freedom® Wireless Grip Dynamometer. This device provides fast, accurate and reliable grip strength evaluation. The wireless grip provides the most convenient way to measure and document grip strength deficits and to evaluate consistency of effort. The dynamometer's wireless interface allows for testing anywhere within a 30-foot radius of the computer. The wireless transceiver has a rechargeable battery and two-way communication to ensure data accuracy.

#### Timed up-and-go Test

The timed up-and-go test was developed more than 20 years ago as a means of measuring changes in mobility over time in the elderly.(100) The test requires documenting the time in seconds that persons "rise from a standard arm chair, walk to a line on the floor 3 metres away, turn, return, and sit down again." The test correlates with measures such as the Berg Balance Scale,(101) gait speed/time, stair climbing, and functional indexes, and has been shown to discriminate between persons according to residential status, falls, and mortality.(102) Reference values have been developed to provide a standardized means of comparing performance between different persons.(102) The timed up-and-go test has also been recommended as a simple screening tool to identify persons at risk of falling.(103)

The test demonstrates good inter-rater reliability in the 40 to 84-year age group, with an intraclass correlation coefficient of 0.94. The test correlates well with age ( $r = 0.36, p < 0.05$ ), gait speed ( $r = -0.64, p < 0.05$ ), and the Berg Balance Scale ( $r = -0.65, p < 0.05$ ).(104)

#### Chair Rise Test

The chair rise test has been shown to be a reliable method for assessing leg strength and balance. The test correlates with walking speed and the ability to perform activities of daily living.(105) The chair rise test requires a combination of muscle power, speed, strength, and balance control,(106) all of which make it a suitable measure of mobility.(107) In a large prospective cohort of 53 year old British men and women, the chair rise test was found to be associated with current weight, physical activity, health status, and socioeconomic conditions.(108)



The chair rise test requires that participants be asked to stand up and sit down from a standard chair as quickly as possible five times in a row, with arms folded across the chest. We record the time using a stopwatch from the initial sitting position (prior to the first stand) to the final standing position (at the end of the fifth stand).

#### Standing Balance Test

Balance is the ability to stay upright or stay in control of body movement. Balance is also an important aspect of agility. To measure balance, participants are positioned approximately one meter from a wall and instructed to stand on one foot for as long as possible while first lifting the dominant leg to the calf level. The test is repeated on the other leg. The test score is the total length of time participants stay in the balance position. The CLSA staffer timing the test serves as a spotter to ensure participants do not lose their balance.

In 52 acute rehabilitation subjects, standing balance was measured using a six-point ordinal scale (0=unable to stand without assistance; 6=able to stand for 30 seconds on either extremity alone) and compared to functional independence measures (FIM) for chair-to-mat transfer, walking, and stairs. Balance and FIM scores had very good agreement (weighted kappa > .85) and FIM scores were correlated with balance cross-sectionally ( $r_s = 0.44-0.77$ ) as well as longitudinally ( $r_s = 0.28$  to  $0.62$ ). In addition, changes in FIM scores were significantly correlated with changes in balance ( $r_s = 0.41-0.60$ ).<sup>(109)</sup> Performance on the balance test was inversely correlated with age in a study of 184 volunteers between the ages of 20 and 79 years. Subjects aged 60 years or over were unable to balance on one leg for as long as subjects aged less than 60 years. Pearson correlation coefficients between age and duration of one-legged balance were  $-0.65$  (eyes opened) and  $-0.79$  (eyes closed).<sup>(110)</sup>

#### Four-metre Walk Test

The four-metre walk test is commonly used in clinical and research settings to measure physical function.<sup>(111)</sup> CLSA participants are asked to walk over a marked, four-metre course at their usual walking pace.

Test-retest reliability of the four-metre walk test over a two-week interval is very good (intraclass correlation coefficient =  $0.79$ )<sup>(112)</sup> and inter-rater reliability is excellent (intraclass correlation coefficient =  $0.93$ ).<sup>(113)</sup> Performance on the four-metre walk test is inversely associated with mortality (hazard ratio =  $0.73$  [ $p < 0.05$ ], adjusted for age, gender, body mass index, cognitive performance, number of clinical conditions, albumin, and total cholesterol).<sup>(111)</sup>

#### *Weight and Height*

Weight and standing (shoeless) and sitting height are measured using a 140-10 Healthweigh digital physician scale and Seca 213 stadiometer. Staff takes two measurements of each variable. Weight data are downloadable onto the CLSA central server immediately; staff read height measurements off analogue rulers and manually enters the data into the computer for download onto the server. The 140-10 Healthweigh and Seca 213 were chosen because of their ease and quickness of use. As well, the 140-10 Healthweigh is capable of weighing persons up to 250 kg (550 lbs.).

#### *Waist and Hip Circumference*

Waist and hip circumference are tape measured around the position of the natural indent in the waist area (halfway between the last floating rib and the iliac crest) and around the largest circumference of

the hips and buttocks (largest protuberance). Staff manually enters measurements, to the nearest tenth of a centimeter (0.1 cm), into the computer for download onto the CLSA central server.

#### *4.4.3. Properties of Questionnaire-based Measures of Physical Functioning Functional Status*

To assess the degree of difficulty CLSA Tracking participants experience in various domains of physical functioning, we are using a set of 28 questions taken from the Framingham Disability Study,(114) Established Populations for Epidemiologic Studies of the Elderly study,(115) as well as the Nagi(116) and Rosow and Breslau(117) scales. These questions and scales have been shown to be reliable and correlated with performance-based measures,(118-122) as well as with lean and fat mass.(123) For the CLSA Comprehensive participants, functional status and performance are assessed using the measures described in Section 4.4.2 above.

#### *Basic/Instrumental Activities of Daily Living*

For all CLSA participants, Basic Activities of Daily Living (ADL) and Instrumental Activities of Daily Living (IADL) are measured using modifications of the questions of the Older Americans Resources and Services (OARS) Multidimensional Assessment Questionnaire.(124) These scales are widely used in research and have been studied in groups of individuals with a broad spectrum of disabilities. Each instrument has seven items that measure ADL. The OARS scale has been extensively validated, demonstrating high correlations with physical therapist measures of self-care capacity (Pearson  $r = 0.89$ ).(125;126) Test-retest reliability and inter-rater reliability are high for both ADL (Spearman  $r = 0.84$ ) and IADL (Spearman  $\rho=0.87$ ).(126)

#### *Life-Space Index*

The Life-Space Index (LSI) is a relatively new instrument that has been designed to evaluate a person's usual pattern of mobility during the month preceding the assessment, integrating both individual functioning and social contexts. The LSI has been shown to be well correlated with functional performance and functional status in terms of ADL.(127-130) The LSI is included in the CLSA Comprehensive Questionnaire.

#### *General Health*

The General Health module administered to all CLSA participants includes one question on each of the following topics: general health, mental health, and healthy aging. The test-retest reliability of single item scales to assess self-rated health is ICC=0.70.(131) There is also recent evidence that mental exercise in older adults is related to improved physical functioning(132) and reduced risk of dementia.(133) To assess mental exercise, the General Health module also includes two questions asking about the frequency of activities such as doing puzzles or playing an instrument/singing in a choir as well as an open-ended question asking participants to explain what factors they believe promote healthy aging.

#### *Injury and Falls*

In the CLSA Tracking and Comprehensive, two questions are used to screen for injuries in the past 12 months. If participants report having had at least one injury during the past 12 months, they are asked the cause, the type of injury, the part of the body that was injured, where they were at the time of injury, what activity was being undertaken, and whether a fracture resulted. These questions are supplemented by a falls module, which focuses specifically on fall-related injuries and their consequences. The injury

module questions have been used in several cycles of the Canadian Community Health Survey (CCHS) and have undergone a rigorous validation process.

#### *Oral Health*

Oral health is measured in the CLSA Tracking and Comprehensive (during the maintaining contact interview) using a questionnaire adapted from the CCHS 2.1 and including oral health status indicators from Locker et al.(134-136) The oral health instrument has seven items about general oral health, teeth/dentures, eating problems, oral health problems, and oral hygiene. The oral health status indicators in the questionnaire have been shown to have acceptable test-retest reliability and internal consistency (all > 0.7), as well as good concurrent and construct validity.(137)

#### *Women's Health*

The CLSA Tracking and Comprehensive includes two questions related to menopause and four questions about hormone replacement therapy. These items were adapted from the Ontario Health Study (OHS).(138)

#### *Pain and Discomfort*

The CLSA maintaining contact interview includes questions about the presence and intensity of pain, as well as whether or not the pain prevents participants from engaging in activities. These questions have previously been used to characterize chronic pain in Canadian adults.(139)

#### *Vision*

The CLSA Tracking and Comprehensive contains three questions about the general condition of one's eyesight and use of aids for visual impairment. The CLSA Comprehensive also includes an in-person vision assessment at the DCS, as described in Section 4.4.2 above.

#### *Hearing*

Four questions in the CLSA Tracking and Comprehensive ask about the general condition of one's hearing, difficulty following a conversation when background noise is present, and use of hearing aids. The CLSA Comprehensive assessment at the DCS also includes an in-person hearing assessment (see Section 4.4.2 above).

#### *Health Care Utilization*

All CLSA participants will be asked eight yes/no questions about contacts with healthcare professionals in the last 12 months. This section will also include additional questions concerning participant visits to emergency rooms, overnight hospital stays, and/or residence in a care facility in the last 12 months. These 11 questions are administered in the maintaining contact questionnaire.

Several studies have shown high agreement between information contained in healthcare utilization databases and seniors' self-reports of hospital stays and contacts with physiotherapists or chiropractors (Kappa  $\geq$  0.68).(140) There is evidence, however, of lower agreement between self-reported family practitioner visits and healthcare utilization database information (Kappa=0.20), although better results have been shown when the recall period is short or there is a significant event that can be used as a reference point. In general, agreement between self-report and information contained in health care utilization databases is adequate for the occurrence of a health care provider contact, but is much more variable for the frequency of utilization.(141) CLSA self-report data on healthcare provider contact will

be supplemented with data from health care utilization databases, enabling us to measure the volume of contact and to validate the self-report data.

### *Medications*

In the maintaining contact interview, one question will be asked of all participants in relation to prescription medication use in the preceding month. A second question asks about the frequency of prescription drug use during this month. Self-reported medication use over a short recall period has been shown to have high agreement with pharmaceutical claims data ( $Kappa \geq 0.75$ ) in telephone interviews.(142)

In the CLSA Comprehensive, participants' use of medications is assessed during the in-home interview. Interviewers ask participants to collect all of their pill bottles/packages prior to the start of the interview. Interviewers confirm participants' medication use by looking at the label and recording the generic (chemical) name and Drug Identification Number (DIN) of each medication. If the generic name is not available, then the interviewer records whatever name appears on the label. The interviewer records the dosage and usage instructions for each medication by looking at the label. In cases where a prescription label reads, "use as directed", the interviewer asks the participant to provide the prescribing physician's directions.

### *Dietary Supplement Use*

Questions to assess calcium, vitamin C, vitamin D, vitamin B12, iron, and multivitamin use are employed in the maintaining contact questionnaire to estimate dietary supplement usage habits. Since the use of herbal supplements in the population is increasing,(143) an item to assess the use of 'other' supplements is also included in the questionnaire. These questions were adapted from the Vitamin and Mineral Questionnaire from CCHS 2.2.(144)

### *Sleep*

An 8-question instrument is administered during the Comprehensive in-home interview to assess participants' sleep habits (Appendix C1, pg 83). The questions cover six domains: participants' satisfaction with the type of sleep they are getting, their actual amount of sleep during the night, whether they have trouble falling asleep or staying asleep, whether they have trouble staying awake when they do not intend to sleep, movements while sleeping, and sensations in the legs while sleeping. The questions were drawn from a variety of sources (145-148) and capture important aspects of sleep and their relation to health. For example, sleep duration has been shown to be an important risk factor for overall mortality and heart disease (148), excessive daytime sleepiness is a screen for disorders such as sleep apnea and narcolepsy, as well as a risk factor for Parkinson's disease and possibly dementia (149), movement while sleeping (rapid eye movement sleep behaviour) is an important risk factor for Parkinson's disease and dementia, with over 50% of affected individuals eventually developing one of these diseases.(150) The questions about leg sensations serve as the basis of screening for Restless Legs Syndrome, which may be an important risk factor for cardiovascular disease and overall mortality.(151;152)

### *Self-reported Height/Weight*

As noted above, for those CLSA participants who come to a data collection site, trained CLSA staff measure height and weight. In the CLSA Tracking, we collected self-reported height and self-reported weight. Specifically we ask about height without shoes in feet and inches or centimetres. Self-reported

weight is collected in pounds or kilograms. Although there is some evidence that under-reporting of weight and over-reporting of height increases with age,(153) methods have been developed to correct for the potential bias.(154)

#### *Chronic Conditions*

The CLSA Tracking questionnaire includes questions asking whether a doctor ever told participants that they had any one of 42 chronic conditions, including respiratory, cardiovascular, neurological, gastrointestinal, rheumatic, mental health, cancer, vision-related and acute conditions. Another four questions ask participants if they saw a doctor for infection. Self-reported, clinician-diagnosed, chronic conditions have been shown to have high test-retest reliability (ICC = 0.96) in population-based health surveys.(155)

CLSA Comprehensive participants are also asked about these same chronic conditions as well as an expanded set of questions for several conditions (e.g., diabetes, stroke, and osteoporosis).

#### *4.4.4 Disease Ascertainment Algorithms*

Diagnosis of chronic diseases requires information from multiple sources, including self-report, physical examination, biospecimens, or imaging. Even with this information, diagnostic uncertainty for many conditions often prevails in clinical practice due to the variable nature of disease presentation. This situation is exacerbated in large-scale population studies because disease ascertainment is often done by non-physicians who possess a limited range of diagnostic tools and little or no ability to consult colleagues or draw on more definitive investigative techniques (e.g., biopsy). To improve assessment of disease in large, population-based studies, researchers have developed disease-specific algorithms.(156;157)

In the CLSA, we do not include physician assessments for the diagnosis of conditions and for this reason, we have developed algorithms that use several pieces of information to ascertain disease. These pieces include the information from the chronic disease symptom questions and the information on medication use. Some algorithms also require physical or biological assessments (e.g., HbA1c test for the diabetes algorithm, pre-bronchodilator spirometry for the chronic airflow obstruction algorithm). Once all of the various pieces of information have been collected, the algorithms serve as ‘pathways’ or guides to combine the information and ascertain participants’ disease classification. Classifications include diseased, not diseased, probably or possibly diseased, or uncertain.

Since the algorithms draw upon many pieces of information that are solely collected in the CLSA Comprehensive (i.e., medication use, physical or biological assessments), we are ascertaining the presence of chronic diseases only for the 30,000 Comprehensive participants. The exception is depression (see below), which is assessed using a questionnaire that is given to both Tracking and Comprehensive participants. Thus, we are ascertaining depression status for all 50,000 CLSA participants.

We are also adding the Parkinsonism questions (see below) to the Tracking maintaining contact questionnaire. This will permit the CLSA to ascertain Parkinsonism status for all 50,000 participants, rather than just the 30,000 Comprehensive participants.

The algorithms are computer programmed and participants' electronically stored data are automatically combined to produce a result for each chronic disease.

The CLSA working groups that developed the chronic disease symptom questions also identified previously published algorithms that would be feasible to use in the CLSA.(158) Algorithms with evidence of concurrent validity were found for all except eight of the chronic diseases. These eight diseases were diabetes mellitus type 2, hand osteoarthritis (OA), hip OA, knee OA, parkinsonism, ischemic heart disease, chronic airflow obstruction (CAO), and dementia.(158) Pilot work to assess the concurrent validity of seven of the algorithms is complete.(159) Validation of the dementia algorithm is ongoing. As well, further validation work is being undertaken to extend the Parkinsonism algorithm to Parkinson's disease, and we are validating a new algorithm for epilepsy.

All of the algorithms are shown in Appendix C3 and briefly described below.

*Diabetes.* The diabetes algorithm classifies all CLSA participants who report taking medications for diabetes as having the disease. For CLSA Comprehensive participants who do not report taking diabetes medications, the HbA1c levels (measured using the blood sample collected at the DCS visit) will be examined to ascertain disease.(160)  $HbA1c \geq 6.5\%$  will indicate diabetes,  $6.0\%$  to less than  $6.5\%$  will indicate possible or probable diabetes, and  $< 6.0\%$  will indicate no diabetes. Our validation work for this algorithm found sensitivities ranging from 95% to 100% and specificities ranging from 70% to 90%.(159)

*Cerebrovascular Event.* The cerebrovascular event (CVE) algorithm uses a modified version of the Questionnaire for Verifying Stroke-Free Status (QVSFS) (161) as an important step for assessing the presence/absence of disease. A 'yes' response to any of the questions on the QVSFS, coupled with patient self-report of a stroke or transient ischemic attack (TIA), indicates the presence of a CVE (symptoms  $< 24$  hours, probable TIA; symptoms  $\geq 24$  hours, probable stroke). A 'yes' to any QVSFS question, but no self-reported stroke or TIA, indicates a possible CVE (symptoms  $< 24$  hours, possible TIA; symptoms  $\geq 24$  hours, possible stroke). 'No' to all QVSFS questions, as well as no self-report, indicate no CVE. No to all QVSFS questions, but 'yes' to self-reported stroke or TIA, means possible CVE.

*Hypo- and Hyperthyroidism.* The hypo- and hyperthyroidism algorithm begins with consideration of whether participants have taken a medication for either condition. If yes, then participants are considered to have disease. If no, then Thyroid-stimulating Hormone (TSH) and thyroxine (T4) levels will be investigated to classify participants according to disease. TSH levels between 0.41 and 4.9 mIU/L will indicate no disease. TSH levels  $\leq 0.4$  mIU/L and thyroxine (T4), with levels between 27.0 and 51.0 pmol/L will indicate subclinical hyperthyroidism while T4 levels  $> 51.0$  pmol/L will indicate definite hyperthyroidism. TSH levels  $\geq 5.0$  mIU/L and T4 levels between 27.0 and 51.0 pmol/L will indicate subclinical hypothyroidism and T4 levels  $< 27.0$  pmol/L will indicate definite hypothyroidism.

*Hypertension.* Systolic blood pressure (SBP)  $\geq 140$  mmHg or diastolic blood pressure (DBP)  $\geq 90$  mmHg indicates hypertension. SBP  $< 140$  mmHg or DBP  $< 90$  mmHg will lead the algorithm to consider participants' self-report of hypertension. If a participant reports hypertension, then her or his current medications are examined to assess disease status. Reported use of anti-hypertensive medication indicates the presence of hypertension. No reported use of medication leads the algorithm to examine

whether diet or exercise is currently being used to control high blood pressure. If so, then the participant is considered to have possible hypertension; if not, then the participant is not considered to have hypertension. In cases where participants self-report no hypertension, the assessment is that hypertension is not present.

*Ischemic Heart Disease.* Myocardial infarction and angina pectoris were combined into a single entity called ischemic heart disease, because of the difficulty in establishing a differential diagnosis between the two conditions. The algorithm for ischemic heart disease contains a series of questions about self-reported diagnosis, prior medical procedures, and medication use, along with electrocardiogram (ECG) results and the Rose Questionnaire.(162) These components are combined to ascertain whether participants have definite, possible, uncertain, or no ischemic heart disease. The Rose Questionnaire is a nine-item instrument containing questions about the presence or absence of pain or discomfort in the chest, the precise location of such pain, and whether the pain persists when walking, standing still, or going uphill. Our validation work for this algorithm found sensitivities ranging from 80% to 100% and specificities ranging from 60% to 95%.(159)

*Osteoarthritis.* The algorithms for identifying OA of the hand, hip, and knee involve a series of queries about self-reported diagnoses, joint enlargement, hand or joint pain, hand enlargement, groin or thigh pain, hip or knee replacement, and pain or swelling in the knees. The questions are grouped according to type of arthritis (hand, hip, and knee). Various combinations of answers to the questions for each type of arthritis determine whether the presence of osteoarthritis is definite, probable, possible, asymptomatic, or uncertain. Our validation work for this algorithm found sensitivities ranging from 65% to 100% and specificities ranging from 85% to 95%.(159)

*Osteoporosis.* Osteoporosis is ascertained by a combination of questions (e.g., self-report of diagnosis, use of medications for osteoporosis, fracture history, back pain) and the results of dual energy X-ray absorptiometry (DXA). For participants who undergo DXA, a femoral neck t-score of  $\leq -2.5$  SD is considered indicative of definite osteoporosis. For participants with DXA scores  $> -2.5$  SD, confirmed low-trauma hip or vertebral fracture and use of medications for osteoporosis are considered indicative of definite osteoporosis. DXA scores  $> -2.5$  SD, low-trauma hip or vertebral fracture, and no use of medications for osteoporosis signify probable osteoporosis. The FRAX<sup>TM</sup> fracture risk assessment tool(163), developed by the World Health Organization, is used in the algorithm. The FRAX score provides a 10-year probability of fracture based on femoral neck BMD, age, sex, BMI, and the number of clinical risk factors such as smoking and alcohol status, history of fractures, exposure to glucocorticoids, and other conditions, such as rheumatoid arthritis.

*Depression.* Depression is ascertained by administering the Center for Epidemiologic Studies Short Depression Scale (CES-D10) (164), which contains 10 questions about items such as feelings of depression, loneliness, hopefulness for the future, and restless sleep. Four possible response options are provided for each question (all of the time, occasionally, some of the time, rarely or never) and the total score may range from 0 to 30. A score of 10 or more indicates depression.

*Dementia.* For dementia, the algorithm is a three-step process involving administration of the neuropsychological battery to develop composite scores in three domains (memory, executive function, psychomotor speed). Participants are classified into five categories depending on the domain scores. The

categories are normal, multiple-domain cognitive impairment-not dementia, amnesic cognitive impairment, single-domain non-memory, and dementia.

*Parkinsonism.* The algorithm for Parkinsonism involves asking participants if they have ever been diagnosed with Parkinson's disease (PD). Affirmative responses to self-reported diagnosis, combined with participant report of taking medications for PD, will lead to ascertainment of 'probable Parkinsonism'. Self-reported diagnosis, coupled with no report of taking PD medications, or no self-reported diagnosis at all, will lead to consideration of responses on a nine-item symptom Questionnaire (165). Response options are dichotomous (yes/no); 'yes' responses are assigned a value of 1 and 'no' responses are assigned a value of 0. Scores < 3 indicate no Parkinsonism, a score of 3 indicates possible or unconfirmed Parkinsonism, and scores  $\geq 4$  indicate probable Parkinsonism. Although the self-report and medication questions, as well as the symptom questionnaire, ask about PD, a diagnosis of PD cannot be made without a clinical examination. Consequently, the algorithm was deemed most appropriate to diagnose Parkinsonism, for which Parkinson's disease is the most common cause. As noted above, this algorithm is currently being validated on CLSA participants using a neurological examination as the gold standard. Our validation work for this algorithm found a sensitivity of 100% and specificities ranging from 95% to 100%.(159)

*Chronic Airflow Obstruction (CAO).* The CAO algorithm includes self-report questions on the presence of symptoms of chronic obstructive pulmonary disease (COPD) or asthma. In the absence of a complete clinical assessment, the CLSA cannot clearly distinguish between COPD and asthma, so the two conditions are combined into an entity called CAO. The CAO algorithm includes consideration of the FEV<sub>1</sub>/FVC (forced expiratory volume in one second/forced vital capacity) ratio, which is derived from the spirometry pulmonary function test. Normal and abnormal FEV<sub>1</sub>/FVC cut-off ratios for each participant are determined in accordance with age- and sex-specific reference values developed from a sample of 7,429 asymptomatic and non-smoking persons from the United States.(166)

Participants who self-report 'no' to COPD or asthma symptoms and have normal-range FEV<sub>1</sub>/FVC ratios are considered non-diseased, regardless of medication use. Participants who report symptoms and have normal-range FEV<sub>1</sub>/FVC ratios are classified as 'possible CAO', regardless of medication use. An abnormal FEV<sub>1</sub>/FVC ratio, irrespective of symptoms, but with no report of medication use, also results in a classification of 'possible CAO'; an abnormal ratio with a positive report of medication use is classified as 'definite CAO'. In the case of participants who self-report 'yes' to the symptoms of COPD or asthma, more algorithm pathways lead to 'definite CAO' to reflect the importance of a positive self-report. Our validation work for this algorithm found sensitivities ranging from 65% to 100% and specificities ranging from 25% to 90%.(159)

#### **4.5. Psychological Functioning**

As people age, their ability to maintain autonomy and social contact, and to perform everyday activities is highly dependent on their level of psychological functioning. Thus, a psychological perspective is a vital component in a longitudinal study of aging. While some large-scale longitudinal studies in psychology have been conducted within the area of adult development and aging, most of this work has focused on the development of specific psychological processes, such as memory and intelligence (e.g., Betula Project), or has occurred within the context of specific diseases or disorders, such as dementia (e.g., Cambridge City Over 75 Cohort Study and Canadian Study on Health and Aging [CSHA]) or heart health (e.g., British Regional Heart Survey, Edinburgh Artery Study), see Appendix A. The CLSA will



expand this research base markedly by examining various psychological constructs as antecedents or mediators of specific and global aspects of health and health-related outcomes.

We use several instruments to measure four domains of psychological functioning: cognition (memory, executive function, and psychomotor speed), mood, psychopathology, and personality traits (openness, conscientiousness, extraversion, agreeableness, and neuroticism) (Table 4.2). The tests comprising the neuropsychology assessment are divided into two batteries. The first set of tests consists of a core battery that is administered to all participants. These tests were selected based on their ability to accurately assess important aspects of cognitive functioning within a relatively short time and are amenable to both telephone and face-to-face administration.<sup>(167)</sup> The tests selected are designed to assess aspects of cognitive functioning that are thought to be vulnerable to increasing age.

The second set of neuropsychological tests supplement those in the core battery either by assessing different constructs or assessing the same constructs in greater detail. Only the CLSA Comprehensive participants receive the second set of tests, which are identified in Table 4.2 and described briefly in the text below. We administer the neuropsychological battery to CLSA Tracking members during the telephone interview and to CLSA Comprehensive members during their in-home and DCS visits.

**Table 4.2. CLSA Psychological Functioning Measures**

Measure	CLSA	
	Comprehensive (n=30,000)	Tracking (n=20,000)
<b>Neuropsychological Exam</b>		
<b>Memory</b>		
Rey Auditory Verbal Learning Test	Q	Q
<b>Executive Function Mental</b>		
Alternation Test	Q	Q
Prospective Memory Test	Q	
Stroop Neuropsychological Screening Test	Q	
Controlled Oral Word Association Test	Q	
Animal Naming	Q	Q
<b>Psychomotor Speed</b>		
Simple and Choice Reaction Times	T	
<b>Mood and Psychopathology</b>		
Depression	Q	Q
Life Satisfaction	Q	Q
Posttraumatic Stress disorder	Q	Q
Psychopathology	Q <sup>1</sup>	
<b>Personality Traits</b>	Q <sup>1</sup>	

Q: measured by questionnaire (either telephone [tracking] or face-to-face [comprehensive] administration).

T: measured using a performance test involving an interactive computer touch screen.

1: measure included in MCQ only.

### *Cognitive Functioning*

Participants in the CLSA Comprehensive complete tests in all three cognitive functioning domains (i.e. . memory, executive function, and psychomotor speed). The tests are administered by a trained interviewer in person and take approximately 27 minutes to administer. The CLSA Tracking participants are assessed on measures of two cognitive functioning domains, memory, and executive function, by telephone only (approximately eight minutes to administer). The tests are scored in a standardized way

using Standard Operating Procedures (SOPs) developed in collaboration with a CLSA co-investigator who is a clinical neuropsychologist.

### *Memory*

#### *Rey Auditory Verbal Learning Test (RAVLT) - (Trial 1 and Delay Trial) (168)*

The RAVLT is a 15-item word learning test that assesses both learning and retention. The list of words is read at the rate of one per second, and records the words in the order in which the participant says them, preferably in an unstructured form to facilitate coding of pattern of recall. For CLSA, one learning trial and one delayed recall trial (with a delay of 30 minutes) is used.

The RAVLT is one of the most widely used neuropsychological test instruments (169) and extensive, normative psychometric data are available for both the English and French versions.(170;171) The RAVLT has been found to have good test-retest reliability ( $0.51 \leq r \leq 0.86$ ) (172), though reliability as low as 0.12 has been reported in one study.(173) The RAVLT has been shown to be extremely sensitive in detecting early cognitive decline.(174;175) Persons with mild cognitive impairment have been found to recall significantly fewer words than normal controls as do individuals diagnosed with probable Alzheimer's disease.(176) Schoenberg and colleagues (177) reported respectable classification accuracy on the delayed recall trial using a z-score cut-off of  $< 1.5$  SD and clinician diagnosis for AD as the criterion (sensitivity=82.9%, specificity=82.8%, PPV=86.2%, and NPV=78.9%).

### *Executive Function*

#### *Mental Alternation Test (MAT) – Subgroup with Trial (178)*

The MAT contains two parts, A and B. Part A requires participants to count aloud from 1 to 20, and say the alphabet as quickly as possible. This part is to ensure that participants can perform these tasks. If they are unable to perform these tasks then the MAT cannot be administered. In Part B, the participant is asked to alternate between number and letter (i.e. 1-A, 2-B, 3-C ...) as quickly as possible for 30 seconds. The number of correct alternations in 30 seconds, discounting any errors, determines the score. The score ranges from 0-51.

The MAT is highly sensitive and specific for detecting cognitive impairment as identified by the Mini-Mental State Examination (MMSE) (179) in older adults. Also, in people with HIV-related cognitive impairment (180;181), the MAT was shown to have 91% sensitivity and 100% specificity for identifying cognitive impairment using the MMSE as the gold standard. Given that the Trail Making Test, a test upon which the MAT is based, is extremely sensitive to progressive cognitive decline in dementia(172), we anticipated that the MAT would be similarly effective.(182)

#### *Prospective Memory Test (PMT)(183)*

There are many ways to assess prospective memory. The CLSA uses the PMT, which contains both event-based and time-based prospective memory tasks that are cued after either 15- or 30-minute delays. The scoring system is based on three criteria: intention to perform, accuracy of response, and need for reminders.

There is increasing evidence that both time-based and event-based prospective memory decline with age (172;184;184;185) and that the PMT has been shown to be sensitive to cognitive impairment. Studies have shown that people with even mild dementia are more forgetful in carrying out future actions (186) and perform poorly in prospective memory tasks.(185) Although correlated with other cognitive

abilities, such as executive function, prospective memory has shown to be a distinct construct (187) and prospective memory deficits have important implications for health (e.g., taking medications), security (e.g., turning off the stove), and economic activity (e.g., checking financial statements).(188)

#### *Stroop Neuropsychological Screening Test (Victoria)(189)*

The Stroop test is a measure of inhibition, attention, mental speed, and mental control. The Golden version (189) of the Stroop test has three parts. In the first part, the participant is asked to read a list of words printed in different ink colours. In the second part, the participant is asked to name the ink color of printed "X"s. In the third part (interference condition), the participant is asked to quickly name the color of the ink that the words are written in and not to read the words (e.g., say "blue" for the word "green" written in blue ink). There are 100 items in a trial for this version. Scoring may be by time, error, both, or the number of items read or named within a specified time limit.

The Stroop test has been shown to have good test-retest reliability(170), but studies on practice and sex effects have shown mixed results.(172) People with Alzheimer's Disease (AD) have been shown to have poorer performance on the interference condition (190;191) and substantial impairment in controlled inhibition tasks.(192) As well, increasing age has been associated with poorer performance on the interference condition. In particular, older adults have been found to be slower in colour naming in the interference condition.(193;194) However, it is unclear whether the observed age effects are due to a general slowing process or to specific impairment of controlled inhibition.(195;196)

#### *Controlled Oral Word Association Test(197)*

This is a measure of phonological fluency or knowledge (i.e., letter-sound associations) and requires the time-limited generation of words that begin with a given letter (e.g., participants are asked to name as many words as possible that begin with the letter "F") Usually three letters are used during three one-minute trials. The score is the total number of admissible words reported.

#### *Animal Naming(178)*

This is a test of verbal fluency requiring participants to name as many animals as possible in 60 seconds.

Letter tests, such as the Controlled Oral Word Association Test, have been found to be discriminative for dementia. Animal naming is also very sensitive to normal cognitive decline and can differentiate normal aging from early-stage dementia.(198) Persons with AD perform more poorly in verbal fluency than letter fluency tasks possibly because of AD-related impairment in semantic knowledge.(199) Verbal fluency measures have also been found to be responsive to age related changes in verbal functioning in prospective studies. Tierney et al.(175), found that animal fluency was an important predictor of incident AD after five years, and Troyer and colleagues (200) found that both clustering and switching scores in verbal fluency tests, including animal naming, discriminate normal aging and dementia. Extensive English and French normative data are available for ages 16-95.(170;201;202)

#### *Psychomotor Speed*

##### *Simple and Choice Reaction Times (RTs) – computer-administered tests (203)*

**Choice Reaction Time (CRT).** In this test participants receive a warning stimulus consisting of a horizontal row of four plus signs on a computer screen. After a delay of 1,000 milli-seconds, one of the plus signs changes into a box. The location of the box is randomly equalized across trials. Participants are instructed to touch the interactive computer touch screen at the location of the box as quickly as

possible. Although the instructions emphasize speed, participants are also instructed to minimize errors. The measures used are the latencies and percent correct for the 52 test trials (there are 10 practice trials).

Choice Reaction Time 1-Back (CRT-1). This task uses the same stimulus display and computer touch screen as the CRT. However, in this version of the task, when the plus sign changes into a box, participants are instructed to touch the screen at the location where the box appeared on the previous trial as quickly as possible. A total of 10 practice trials and 52 test trials are administered. Because participants make no response on Trial 1, the remaining 51 test trials are used for analysis.

Reaction times increase and become more variable with age.(204;205) Simple reaction time tends to increase slowly in the 50s and 60s and then sharply after the 70s (206;207), whereas slowing in choice reaction time occurs throughout adulthood and into later life.(206) Simple reaction times have been shown to distinguish normal controls from older adults with dementia; and reaction times have been shown to vary more in individuals with mild dementia than in controls.(208) The increase in inconsistency in reaction times has been found to be predictive of cognitive performance (209) and can be used to discriminate between persons who are aging normally from persons who are in the early stages of dementia.

#### *Mood and Psychopathology*

Research published to date suggests that complex associations exist between positive and negative mood states, psychopathology and physical and mental well-being.(210;211) It has been suggested that negative emotional states in themselves increase susceptibility to an array of health conditions and are associated with poorer prognoses. For example, the effect of various negative emotions appears to significantly influence immune function and regulation (which become less efficient in later life), thus increasing the risk of a myriad of health conditions.(212)

Social science research has been criticized for equating well-being with the absence of psychopathology (e.g., Stoller & Pugliesi(213); Stull et al.(214)). In other words, persons deemed to be free of psychiatric distress were assumed to be well, happy or satisfied with life. Implicit in such studies was the assumption that emotional experience existed along a single continuum. However, more recent research indicates that psychological well-being and psychopathology (and their correlates) are somewhat independent phenomena.(215) Therefore, to assume the existence of one on the basis of the absence of the other is empirically unsupported; both need to be assessed in order to arrive at a balanced understanding of emotional wellness.

#### *Negative Mood State*

Depressive symptoms are measured in the CLSA Tracking and Comprehensive using the short form of the Center for Epidemiologic Studies – Depression (CES-D10) Scale.(164) The CES-D10 takes approximately three minutes to administer and is one of the best-known instruments for identifying symptoms of depression and has been used extensively in large studies. Both the Health and Retirement Survey (HRS) and its sister survey, the English Longitudinal Study on Aging (ELSA) employed the CES-D10 short form to measure depressive symptoms. The CSHA also used the full CES-D and the Andresen short form. Across adult samples, internal consistency of responses to the CES–D has been estimated to be within optimal values for both community and clinical samples (e.g., Cronbach's  $\alpha =$

0.85 to  $\alpha = 0.91$ ).(178) The 10-item Andresen short form shows close agreement with the full version ( $\kappa = 0.97$  and a test-retest reliability of 0.71).(164)

#### *Positive Mood State (Life Satisfaction)*

Satisfaction with life is measured using the Satisfaction with Life Scale (SWLS).(216) The SWLS is comprised of five questions and takes about 90 seconds to administer. The SWLS is one of the most widely used scales to measure the life satisfaction component of subjective well-being and has excellent psychometric properties including high internal consistency ( $.79 \leq \alpha \leq .89$ ) and test-retest reliability ( $.50 \leq r \leq .84$ ).(217;218) The SWLS can be used with adults of various ages and has been validated in French.(218) In addition, SWLS has been used in other international longitudinal studies including the ELSA and thus would allow for both intra- and inter-national comparative analyses.

#### *Posttraumatic Stress Disorder (PTSD)*

The prevalence of lifetime PTSD in Canada has been estimated at 9.2%.(219) There are a number of screening instruments for PTSD of varying length. In a systematic review, Brewin reported that instruments with fewer items and simpler response scales performed as well as longer more complex measures.(220) The CLSA includes the four-item primary care PTSD (PC- PTSD) screening instrument to measure PTSD. The PC-PTSD demonstrated excellent sensitivity (78%) and specificity (87%) when compared to a more extensive clinician-administered scale as a reference standard and takes about 30 seconds to administer. The CLSA has included this short tool as part of the CLSA-Veterans' Health Initiative in which a set of Veteran Identifier questions are asked to all CLSA participants.

#### *Psychopathology*

Non-specific psychological distress is measured using the Kessler Psychological Distress Scale (K10).(221) The K10 was developed using item response theory to maximize discriminant ability at the severe range of psychological distress. The Kessler scale is becoming one of the most widely used screens for psychological distress in epidemiological surveys. It has been used successfully in national population health surveys in the U.S (NHIS), Canada (CCHS 1.2), Australia (NSMHWB), and across the globe under the WHO World Mental Health Survey Initiative. The K10 has high internal consistency with Cronbach's alphas ranging from 0.89 to 0.93(221) and have been shown to predict diagnosis of serious mental illness.(222) As a screening tool the K6 and K10 have shown good diagnostic accuracy ( $AUC > 0.85$ )(221;223;224) which is not biased by sex or by level of education. In the CLSA, we will use the K10, which takes approximately two minutes to administer and is included only in the Comprehensive Maintaining Contact questionnaire.

#### *Personality Traits*

Personality traits are "enduring patterns of perceiving, relating to, and thinking about oneself and the environment that are exhibited in a wide range of social and personal contexts". (225)The Big Five personality traits are five broad domains of personality (openness, conscientiousness, extraversion, agreeableness, and neuroticism) that have been the most extensively researched model of personality(226), and have been widely shown to be related to self-rated health.(227)

The CLSA measures personality traits using the Ten-Item Personality Inventory (TIPI).(228) This instrument has two items per Big Five dimension. The TIPI has shown satisfactory convergent validity when correlated with the 44-item Big Five Inventory(226)(correlation ranging from 0.65 to 0.87) and

test-retest reliability ( $r=0.72$ ).<sup>(228)</sup> The TIPI takes approximately one minute to administer and is included only in the Comprehensive Questionnaire.

#### 4.6. Social Functioning

Social functioning emphasizes issues of sustained engagement with life, the essential characteristic being the interaction between the individual and society.<sup>(236)</sup> Exchanges between individuals and society all contribute to social functioning. These are facilitated through family and other social ties, employment and retirement, and are influenced by access to structural supports such as housing, transportation, community resources and health services. Based on current knowledge, we have included four key domains in the CLSA questionnaire: social networks (including online social networking) and social support, social participation, informal and formal care, transitions in work and retirement, social inequalities and wealth, and matters of place (including migration, transportation and the built environment), Table 4.3. All measures are included in the baseline questionnaire unless otherwise noted.

**Table 4.3. CLSA Social Functioning Measures**

Measure	CLSA	
	Comprehensive (n=30,000)	Tracking (n=20,000)
Social Networks	Q	Q
Online Social Networking	Q <sup>1</sup>	Q <sup>1</sup>
Social Support Availability	Q	Q
Social Participation	Q	Q
Care Receiving 1/ Formal Care	Q	Q
Care Receiving 2/ Informal Care	Q	Q
Care Giving	Q	Q
Retirement Status	Q <sup>2</sup>	Q
Pre-Retirement Labour Force Participation	Q <sup>2</sup>	Q
Labour Force	Q <sup>2</sup>	Q
Retirement Planning	Q <sup>2</sup>	Q
Social Inequality	Q <sup>1</sup>	Q <sup>1</sup>
Wealth	Q <sup>1</sup>	Q <sup>1</sup>
Transportation, Mobility, Migration	Q <sup>1</sup>	Q <sup>1</sup>
Built Environments	Q <sup>1</sup>	Q <sup>1</sup>

Q: measured by questionnaire (either telephone or face-to-face administration)

<sup>1</sup>Measure included in Maintaining Contact Questionnaire only

<sup>2</sup>The CLSA Comprehensive will include an abbreviated module

#### *Social Networks and Social Support*

The CLSA Questionnaire includes 15 items pertaining to the respondent's social network which measures marital/partner status, living arrangements, family composition, social ties, and social contacts.

These items were adapted from the General Social Survey (GSS) (cycles 1, 5, 11, 16) and reflect items widely used within relevant literature. Social support is multidimensional and includes the perception that one is in receipt of emotional support, instrumental assistance, information, guidance and feedback, personal appraisal support, and companionship. It is measured using the 19-item MOS Social Support Survey.(237) Although originally developed for use in clinical studies of chronically ill patients living in the community, items are considered universally applicable.(238) The scale takes approximately six minutes to administer and has demonstrated excellent internal consistency (overall and subscale Cronbach alphas ranging from 0.91 to 0.97), test-retest reliability (ICC = 0.78 after 1 year), and convergent validity, showing moderate to strong correlations with loneliness ( $r = 0.53$  to  $0.69$ ), marital and family functioning ( $r = 0.38$  to  $0.57$ ) and mental health ( $r = 0.36$  to  $0.45$ ).(238). We have also included a module to supplement social networks to assess on-line communication and use of internet social networking sites.

#### *Social Participation*

In the CLSA, social participation is measured using questions describing the frequency of participant involvement in social activities (e.g., family or friendship activities, church, sports/physical activities, educational or cultural activities). These items were used in the CCHS-Healthy Aging(239) and ELSA(240) and have gone through rigorous development and testing. The full module takes approximately 3 minutes to administer.

#### *Informal and Formal Care*

In the CLSA, informal care is defined as the performance of tasks by family members, friends, or neighbours in response to a health condition or limitation that affects daily activities. Formal care is defined as the performance of these same tasks by a professional service provider. Informal and formal care receiving and care giving are measured using items adapted from the General Social Survey (GSS) (cycles 11, 16 and 21).(241) They are similar to items used in the CCHS- Healthy Aging. Both the GSS and CCHS items have gone through rigorous development and testing by Statistics Canada. Questions regarding other types of formal care (e.g., physician visits, hospitalizations, alternative medicine use) are included in the Health Care Utilization module of the CLSA Maintaining Contact Questionnaire. The informal and formal care receiving and care giving modules each take about two minutes to administer.

#### *Transitions in Work and Retirement*

The CLSA Questionnaire measures current labour force participation or labour force participation prior to retirement (depending on the participant's retirement status), reasons for retirement, retirement planning, and work ability. We collect both occupation and industry of the current (or last) occupation and the job held for the longest time. These were adapted from questions used the GSS (cycles 9, 16, 21) and other international surveys (ELSA, HRS, SHARE). Work ability is measure using the Work Ability Index.(242;243)The labour force participation module (either current or pre-retirement) takes about three minutes to administer. The retirement status and retirement planning modules take about two minutes each to administer. An abbreviated version of these modules will be used in the Comprehensive Cohort questionnaire.

### *Social Inequalities and Wealth*

Within the CLSA, socioeconomic status (SES) is measured as a multidimensional concept, and will include relatively objective indicators of educational attainment, type of employment and hierarchical position in the workplace, income, and wealth. Wealth is measured by 12 questions about current income, investments, assets, and debt drawn from ELSA and Survey of Health, Aging and Retirement in Europe (SHARE). Questions were modified to reflect the Canadian context. These questions take four minutes to administer. Other aspects of SES are collected in the demographics section of the CLSA questionnaire. Social inequality is measured using the MacArthur Scale of Subjective Social Status.(244) The scale is presented as a 10-rung "social ladder" and participants are asked on which rung they feel they stand. The scale takes one minute to administer, is well validated and has been shown to predict health status and decline in health status over time in middle-aged adults.(245;246) Wealth and social inequality modules are included in the Comprehensive and Tracking Maintaining Contact questionnaire.

### *Matters of Place - Migration, Transportation and the Built Environment*

The CLSA Maintaining Contact Questionnaires include measures relevant to the domains of migration, mobility, and built environment. These include 3 questions on migration adapted from the Centre of Aging, University of Victoria Baseline Survey of Seniors (247) and six questions on mobility and transportation that came from 'The Older and Wiser Driver' questionnaire.(248) Finally, a series of 11 questions regarding individuals' perceptions of their neighbourhood, including disorder (e.g. vandalism and graffiti) and cohesion (e.g. feeling part of the area) also drawn from the HRS is included. The transportation/migration and built environment modules each take about two minutes to administer.

## **4.7. Lifestyle, Behaviour and Socio-Demographic Content**

### *Lifestyle and Behaviour*

Lifestyle factors play a significant role in successful aging through their link to virtually every major disease or condition affecting an individual. For example, the high incidence of type 2 diabetes mellitus, is clearly labelled as lifestyle pathology.(249) A sedentary lifestyle leads slowly and inexorably to diminished muscle strength and frailty, so that at age 70 and beyond, the average individual is confronted with decreased movement capacity, increased risk of falling, and an increased risk of being injured in falls or other accidents. Nutritional problems, either insufficient(250) or excessive(251) calories, have frequently been linked to the development of frailty. The research literature has demonstrated that unhealthy lifestyle behaviours result in three- to fourfold increases in premature mortality.(252) On the other hand, health benefits associated with improved lifestyle can be observed at all ages.(253) The CLSA Questionnaire includes measurement of physical activity, nutritional risk, tobacco consumption, and alcohol consumption.

### *Physical Activity*

In the CLSA Tracking and Comprehensive Maintaining Contact Questionnaires, physical activity is quantified using the Physical Activity Scale for the Elderly (PASE) questionnaire.(254-258) Individuals are asked to report leisure time activity (6 questions), household activity (3 questions) and work-related activity (1 question) in the past week. This physical activity questionnaire was chosen because it reflects



traditional domains of physical activity (e.g., light, moderate, and strenuous sports or recreational activities), but also reflects types of activities more commonly performed by elderly people (e.g. walking and sitting activities). Daily averages of time spent doing each activity are summed and weighted by intensity. A global score is assessed from energy expenditure coefficients for each activity recorded. This calculation allows for the calculation of METS. Although the PASE was developed for an elderly population, it has also been used in studies including middle-aged participants.(259-261) The PASE takes approximately six minutes to administer and has good reliability (test-retest reliability = 0.75).(254) Convergent validity has also been demonstrated ( $r = 0.68$ ) through correlation with energy expenditure in 60- to 80- year olds measured using Doubly-Labelled Water.(257)

### *Nutrition*

Nutritional risk is assessed in the CLSA Tracking Maintaining Contact interview using the abbreviated version of the SCREEN II.(262) This 11-item instrument takes three minutes to administer and has been validated in the community-dwelling elderly. The SCREEN II has demonstrated good sensitivity and specificity compared to dietitians' assessment of nutritional risk ( $AUC \geq 78\%$ ) and adequate test-retest and inter-rater reliability ( $ICC = 0.83$  for both).(262) In addition, we are collecting information on frequency of fast-food consumption, coffee and tea consumption, and on food security.

Nutrition is measured in the CLSA Comprehensive in-home interview using the Short Diet Questionnaire (SDQ) (263) (Appendix C1), which is a food frequency questionnaire designed to measure intake of total fat, fatty acids, cholesterol, trans fat, dietary fibre, calcium and vitamin D, and servings of fruits and vegetables. The SDQ was developed in response to concerns about suboptimal intakes of several key nutrients and foods among adults, as well as inherent difficulties in administering a full food frequency questionnaire (FFQ) to elderly individuals.

The SDQ incorporates the six fruit and vegetable questions from the Behavioural Risk Factor Surveillance System Survey Questionnaire (<http://www.cdc.gov/BRfss/questionnaires.htm>) into the SDQ food list, and is composed of 30 food and six beverage items. It queries subjects' usual intake frequencies in the previous 12 months.

Correlations between the SDQ and recalls were positive and statistically significant ( $p < 0.01$ ) and ranged from  $r_s = 0.17$  (n-3 fatty acids) to  $r_s = 0.45$  (fruits and vegetables). Cross-classification into quartiles showed that for all nutrients combined, 33% were jointly classified into identical quartiles of the distribution, 73% into identical and contiguous quartiles, and only 7% were misclassified; no differences emerged by sex.

We chose the SDQ because it can be used to collect a substantial amount of information about key nutritional concerns within a relatively short ( $\leq 10$  minute) administration time. This balances our data collection requirements with the need to avoid participant burden. The SDQ is the only dietary instrument that achieves this balance and that has been validated in the Canadian population.

### *Tobacco Consumption*

The CLSA includes 23 items measuring tobacco consumption (current and former smoking habits) and environmental smoke exposure. The module takes approximately two minutes to administer. The validity of self-reported smoking is consistently high in population-based studies.(264) The items included in the CLSA Questionnaire were adapted from those used in the OHS(138) which were

originally sourced from the Canadian Health Measures Survey (CHMS)(265) and the Canadian Tobacco Use Monitoring Survey (CTUMS)(266), which are both current, reliable sources.

#### *Alcohol Consumption*

The CLSA Questionnaire includes six items measuring the amount and type of alcohol consumed in the past 12 months and ever. The questions take one minute to administer. The items were adapted from the OHS(138) which were originally sourced from the Centre for Addiction and Mental Health Monitor.(267)

#### *Socio-Demographic Information*

Demographic information is collected in the CLSA for two purposes. Comparing the demographic profile of our sample with the Canadian population between the ages of 45 and 85 years will allow us to assess potential selection bias. As well, demographic factors are related to a large number of health outcomes, both directly and as mediators. The CLSA questionnaire includes items on sex, age, education, income, ethnicity, language, and religion. The demographic items have been adapted from those administered in the CCHS Healthy Aging and take about two minutes to administer.

### **4.8. Secondary Data Collection**

#### *4.8.1. Individual Level Data*

In jurisdictions where permitted, the primary data of all CLSA participants who provide a health insurance number and signed consent for linkage will be linked to existing health care administrative databases (e.g., drug plans [for those aged 65 years and over or those who are on social assistance], physician visits, medical service plans, hospitalization, homecare, and mortality). The purpose of these linkages will be to collect complementary information on medication use and health services resource utilization, as well as to ascertain deaths and causes of death.

There are many practical, methodological, and ethical issues involved in using provincial healthcare registration databases for research. Each province has a unique set of data liberation requirements that makes obtaining a common set of health indices across provinces challenging. Recognizing this issue, the CLSA investigators have done extensive preparatory work to learn about the province-specific regulations and engage provincial data stewards and privacy commissioners to help facilitate the data linkage process.(268) In addition a working group composed of the data stewards and CLSA researchers has been formed to support the process of sample selection and health care utilization data acquisition. Most recently, in September 2011, a workshop was held to bring together investigators from large Canadian cohort studies (CLSA and the Canadian Partnership for Tomorrow Project) and data custodians from each provincial ministry of health to address challenges and opportunities related to a pan-Canadian linkage program.(269)

#### *4.8.2. Contextual Data*

An important contribution of the CLSA will be to combine primary data collected at the individual level (e.g., physical performance measures) with contextual data collected at aggregate levels. Several agencies, including the Federation of Canadian Municipalities (FCM), the Institute of Medicine (IOM) in the U.S. and the U.S. National Committee on Quality Assurance, have proposed methods for selecting manageable sets of high-quality indicators that can be used to measure elements of the population's health.(270) With this in mind, we have chosen to adopt the IOM criteria for selecting a subset of indicators for social cohesion, urban and neighbourhood characteristics and environmental quality.

These criteria are: (1) relevancy across a broad range of communities and population subgroups, (2) responsiveness to change, (3) balance between environment, economy and social aspects, (4) ease of collection and reliability and (5) consistency with research objectives, in this case, successful aging.

Indicators for social cohesion will include voter turnout, recycling rates, volunteer organization per capita, newspaper readership, stability, charitable donations, and feelings of safety. The indicators of neighbourhood quality will include general economic base and status, neighbourhood type (e.g., ratio of private homes to businesses), amenities for older people, rental costs, vacancy rates, shopping facilities, crime rates, and vandalism. The indicators for environmental quality will include green space per capita, air and water quality and climate.

The sources of social cohesion, neighbourhood, and environmental quality data will include Statistics Canada, Environment Canada, police reports and provincial and municipal data. For the purposes of linkage with contextual data, the CLSA will record the six-digit postal code of every participant. The Statistics Canada Postal Code conversion file will be used to aggregate postal codes up to census tracts and enumeration areas and to provide latitude and longitude for climate analyses. The choice of geographical unit of analysis will depend on the nature of data (e.g., larger areas would be more appropriate in analyzing air quality data, whereas smaller areas would be used for assessing the quality of neighbourhoods).

## SECTION 5: RESEARCH DESIGN AND METHODS

### 5.1. Study Design

The CLSA is a population-based, 20-year, prospective cohort study. The study is recruiting 50,000 men and women aged 45 to 85 years, at the time of recruitment, from the Canadian population. The 50,000 individuals comprising the CLSA are selected into one of two study components (i.e., the CLSA Tracking and Comprehensive), which use different sampling designs (see below for a more complete description of the two components). Participants undergo repeated waves of data collection every three years and will be followed for at least 20 years, or until death. The choice of three years balances the need to have a short enough interval to capture important changes and map trajectories with the practical consideration of the time required to complete a wave of data collection. Scheduled follow-up visits are supplemented with a brief inter-assessment telephone interview (Tracking or Comprehensive Maintaining Contact Questionnaire) to collect some additional data as well as to update contact information, thereby minimizing loss to follow-up.

The inclusion of study participants as young as 45 years of age at baseline is motivated by the desire to capture mid-life experiences prospectively, since important changes known to influence outcomes later in life occur during this period. For example, mobility limitations in mid-life are associated with an increased risk of falls and frailty in later-life in the physical health domain and with social isolation and depression in the psychosocial health domain. The lower age limit also permits inclusion of individuals who are part of the baby boom cohort (i.e., those born between 1946 and 1964), who were 47 to 65 years of age at the onset of recruitment in 2011. The upper age limit includes individuals entering their senior years who are making the transition into retirement, those who are already retired, and those who have already reached older age. One of the interests in studying the oldest age group prospectively is to examine transitions into the final years of life.

Study subjects who are part of the CLSA Comprehensive are asked to provide information through questionnaires (Main-wave In-home Questionnaire, Main-wave DCS Questionnaire), physical examinations, and biological samples. Owing to the technical demands for this type of data collection (e.g., in-person examination, biological sample storage and shipping facilities) individuals included in the CLSA Comprehensive are recruited from people who live within a 25 to 50 km radius of 11 major academic centres across Canada. These locations were selected to represent four regions of Canada: the Pacific Coast (Victoria [University of Victoria], Vancouver and Surrey [University of British Columbia and Simon Fraser University]), the Prairies (Calgary [University of Calgary] and Winnipeg [University of Manitoba]), Central Canada (Hamilton [McMaster University], Ottawa [University of Ottawa], Montréal [McGill University] and Sherbrooke [Université de Sherbrooke]), and the Atlantic Region (Halifax [Dalhousie University], and St. John's [Memorial University of Newfoundland]). Sampling in most locations is restricted to a 25-kilometre radius; however, in locations with smaller population densities (i.e., Victoria, Sherbrooke, Halifax, St. John's), the radius may be expanded to 50 kilometres to facilitate capture of the necessary number of participants. Each DCS is responsible for recruiting 3,000 participants, except in Vancouver and Surrey, where the University of British Columbia and Simon Fraser University DCS share a region and each recruit 1,500 participants to provide a sample of 3,000 for the Vancouver area.

While the administrative and infrastructure requirements of the CLSA Comprehensive require a sampling strategy that will not result in a nationally representative sample of the population of Canada,

it is, nevertheless, national in scope. The primary aim of the CLSA Comprehensive is to provide longitudinal information to answer analytical research questions requiring in-depth data. The target sample size for the CLSA Comprehensive is 30,000 persons.

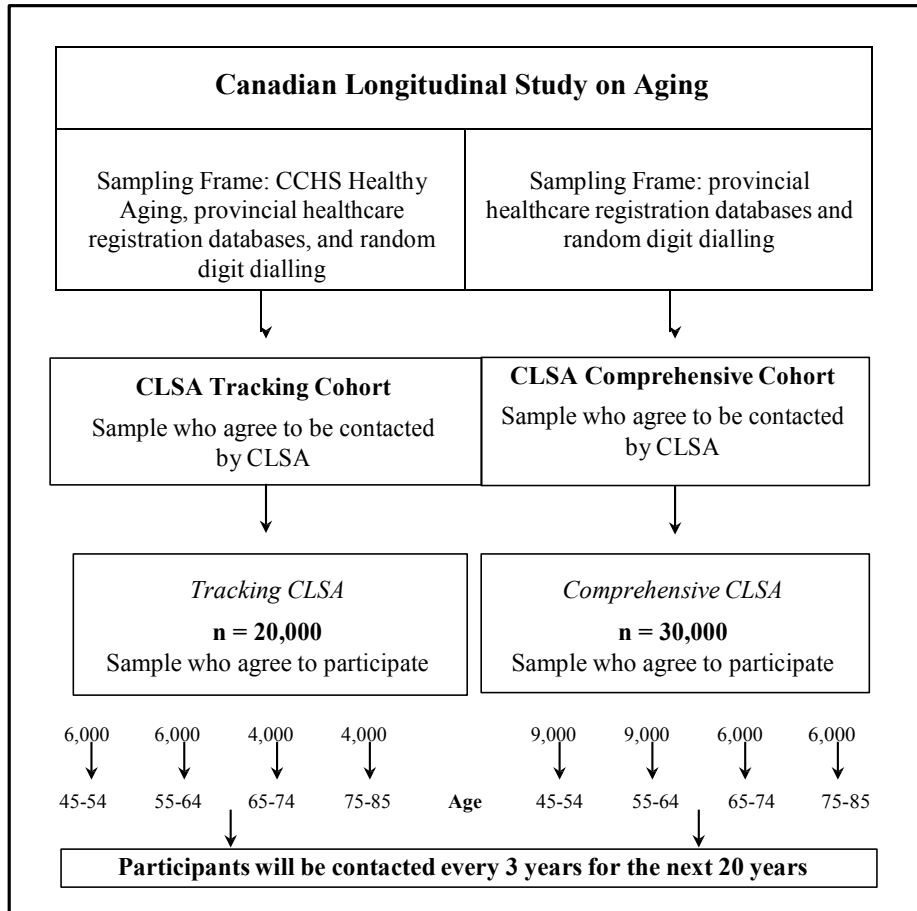
Study subjects who are part of the CLSA Tracking, on the other hand, participate in the CLSA primarily through computer-assisted telephone interviews (CATI). CATI was used to administer the Tracking Recruitment Questionnaire for participants recruited through the CCHS Healthy Aging survey, and is being used for the Tracking Main-wave Questionnaire, and will be used for both the Tracking and Comprehensive Maintaining Contact Questionnaires. The members of the CLSA Tracking are sampled to be representative of the population of Canada and to permit precise provincial level cross-sectional estimates of health determinants, health status and health system utilization. The primary aim of the CLSA Tracking is to address issues pertaining to both current policy and the determination of future policy. The target sample size for the CLSA Tracking is 20,000 persons.

At the beginning of the protocol development for the CLSA, the original plan was to recruit a cohort of 50,000 study subjects who would all undergo extensive data collection along the lines of the Comprehensive CLSA. As a result of numerous discussions with, and input from, co-investigators, partners and advisors, a decision was taken to modify the design to include the two CLSA components as briefly described above. Several considerations contributed to this design modification:

- If all 50,000 study subjects were to be examined in person and asked to undergo blood and urine sampling, the sample of participants could not be selected from rural centres.
- A sampling strategy restricted to areas surrounding major academic centres would preclude the generation of provincial level estimates of health and social parameters of interest to policy makers, a key objective of the study.
- One of the most expensive aspects of the study would be the collection, preparation, shipping, and analysis of biological specimens, and the total cost of 50,000 such samples collected regularly over a 20-year period would be prohibitive, especially from remote rural areas of Canada.

The current design retains an important feature of the original design—that is, the inclusion of a large sample (30,000) of subjects from whom extensive data will be collected with the aim of responding to scientific questions (the CLSA Comprehensive). The development of a second cohort is an innovative modification to the design. This second cohort (the CLSA Tracking), for whom data are collected through CATI, does not require the study subjects be selected in proximity to major academic centres. Subjects are selected in such a way as to be a representative national sample, and this will permit the estimation of the health and social parameters both cross-sectionally and longitudinally as desired for policy-relevant outcomes. Furthermore, using an identical follow-up schedule for the two cohorts with the collection of overlapping information, the CLSA Tracking and the CLSA Comprehensive can be used for specific analyses that require larger sample sizes than is present in each cohort but that do not require the depth of data collection obtained in the CLSA comprehensive. See Figure 5.1 for additional details.

**Figure 5.1. CLSA Study Design**



**5.2. The Sampling Frame and the Sample**

Several sampling frames for the CLSA were considered, including administrative records such as provincial healthcare registration databases, telephone directory listings and the census. The use of random digit dialling was also entertained as a means to create a sampling frame. Neither use of telephone directory listings nor random digit dialling can fully guarantee that (1) each individual in the target population is in the sampling frame or (2) that each individual has a positive probability of being selected; thus, there is a potential for a biased frame. For these reasons, these two options were not considered as the primary mode of sampling.

To select a sampling frame, the CLSA team initially collaborated with Statistics Canada to assess the feasibility of using the census or the labour force survey frame (LFS), the latter is also based on the

census, as potential sampling frames.(271) In doing so the CLSA was able to build upon Statistics Canada's methodological expertise and experience in the conduct of large Canadian population surveys. The CLSA team concurrently investigated the possibility of using provincial healthcare registration databases as a sampling frame.(268) After consideration of the possibilities, and pilot work, it was determined that the best option to recruit subjects into the CLSA Tracking was to use Statistic Canada's Canadian Community Health Survey (CCHS) 4.2 on Healthy Aging as the initial enrolment platform. The use of provincial healthcare registration databases was proposed as a second source to make up the remainder of the CLSA Tracking, as required, and for the CLSA Comprehensive. The use of random digit dialling was reserved as a backup, as required.

#### *5.2.1. The Canadian Community Health Survey (CCHS) Healthy Aging*

The CCHS is a survey instrument developed by Statistics Canada to produce cross-sectional estimates of health determinants, health status, and health system utilization for health regions and provinces in Canada.(272) Up to 2007, the CCHS comprised two cross-sectional surveys conducted over a two-year, repeating cycle. In the first year of each cycle, the sample size is large (~130,000) since the goal is to provide estimates at the level of 136 regions, while in the second year of the cycle, the data are collected to provide estimates at the provincial level, with a correspondingly reduced sample size (n~30,000). The purpose of cycle 4.2 CCHS-Healthy Aging was to collect new information about the factors, influences, and processes that contribute to healthy aging through a multidisciplinary approach focusing on health, social, and economic determinants. The survey questionnaire was developed collaboratively with the CLSA research team and focuses on the various factors that impact healthy aging, such as general health and well-being, physical activity, use of health care services, social participation, as well as work and retirement transitions. The target population of the CCHS Healthy Aging was originally people aged 55 and over living in private dwellings in the ten Canadian provinces. The CCHS Healthy Aging used the 2006 census as an area frame to select a sample of households. As part of the Statistics Canada – CLSA collaboration, an additional sample of individuals aged 45-54 was included in the CCHS Healthy Aging to include the full age range of the CLSA.

#### *5.2.2. Census as a Sampling Frame*

##### *5.2.2.1 Sample Size and Allocation*

To meet their objectives, Statistics Canada proposed a sample of 32,005 responding units for the CCHS Healthy Aging. A two-step strategy was used to allocate the sample to the provinces. First, 125 sample units were allocated to each domain of interest (10 age/sex groups) in each province. Thus, 1,250 units were assigned to each province in the first step for a total of 12,500. The remaining 19,505 units were allocated to the provinces using a power-allocation method.(273) Essentially, this power-allocation method is used when separate estimates are of interest for the strata (i.e. provinces), as well as for the entire population. Using this method, each stratum's component of the variance of the estimated population total receives a weight. The sample is then allocated by minimizing this weighted function. The total sample size of any given province is found by adding the sizes obtained in the two steps.

To have reasonable urban and rural representation in each province, the provincial sample was subsequently proportionally allocated to two strata, urban and rural, according to the number of dwellings having people aged 45 and over in each stratum. Then sample sizes were inflated before data collection to take into account out-of-scope and vacant dwellings and anticipated non-response.

#### 5.2.2.2. *Sampling of Households*

In this section, we describe the methodology used by Statistics Canada for the overall CCHS on Healthy Aging. This description includes mention of those recruited over the age of 85 into CCHS Healthy Aging but it is of note that CCHS participants over the age of 85 were not considered for inclusion into the CLSA. All dwellings within each province containing at least one household member aged 43 and over (i.e. those who would be aged 45 and over in 2008) were included in the sampling frame. All dwellings within the same Census dissemination area block (CB), identified as either urban or rural were grouped together. In each province, clusters of CBs were created having a fixed number of dwellings with a minimum number of people in the 75-84 and 85 or over age groups. Clusters were composed entirely of urban or rural CBs and could not cross provincial boundaries. Some remote and empty CBs were excluded from this process.

Each urban cluster yielded approximately 35 dwellings, and each rural cluster yielded approximately 20 dwellings. The number of each type of cluster to select in each province was determined by the urban/rural proportion of dwellings from the 2006 Census having a household member aged 85 or over. For each province, the selection of clusters was done with probability proportional to size (number of dwellings in each cluster having a household member aged 45 or over) without replacement using the Hanurav-Vijayan algorithm.(274)

Dwellings in each cluster were further stratified into three groups: first, dwellings having a household member aged 85 or over; second, dwellings with only household members aged 45-54; and third, all other dwellings. The number of dwellings to select in each stratum was fixed for all provinces, with a slight adjustment made for Québec and Ontario.

#### 5.2.2.3. *Sampling of Individuals*

Upon visiting a dwelling, all members of the household were listed and one person aged 45 years or over was automatically selected using selection probability factors based on age. There were five selection probability factors dependent on age: 45-54, 55-64, 65-74, 75-84 and 85 or over. The selection probabilities varied by province in order to achieve the targeted number of respondents in each age group.

#### 5.2.3. *CLSA Pilot Studies*

In collaboration with Statistics Canada, CLSA investigators conducted two pilot studies to obtain estimates of the response rates expected in the CLSA. The first study, conducted in 2004 (271), examined the proportion of CCHS Healthy Aging pilot respondents who would be willing to: 1) share their names and addresses with the CLSA and 2) share CCHS Healthy Aging survey responses with the CLSA. We found that 64% of the CCHS respondents agreed to share their contact information with the CLSA and 76% were willing to provide their CCHS survey responses to the CLSA. One of the limitations of this study was that only those CCHS pilot participants who were willing to share their data with Health Ministries and the Institut de la Statistique du Québec were asked the CLSA sharing questions. However, this is not likely to create significant bias because 94 percent of the eligible CCHS pilot participants agreed to share their survey data with the health ministries and the Institut de la Statistique du Québec.(271)

During a second phase of pilot testing (conducted in 2009), the same CLSA sharing questions were asked of a subsequent group of CCHS Healthy Aging pilot respondents. Of the 596 CCHS pilot



participants, 258 were willing to share their contact information and their CCHS survey responses, 18 were willing to provide their contact information, but not their CCHS data, 198 were willing to share their CCHS data but not contact information, and 122 were not willing to share either; thus in total 46% of the CCHS Healthy Aging pilot participants were willing to share their contact information with the CLSA. Those willing to share their contact information were then approached by CLSA interviewers to pilot test the recruitment methods and the CLSA questionnaire. Of the 276 (258+18) potential participants, 140 (51%) agreed to participate in the CLSA pilot and completed the interview. We considered this response rate to be an underestimate for the following reasons: the pilot study was conducted in the absence of any media campaign to publicize the CLSA; and potential participants were not contacted until approximately one year after they had completed the CCHS Healthy Aging pilot interview. For the actual study, a media campaign preceded recruitment, when possible, and every effort was made to shorten the interval between the CCHS Healthy Aging interview and recruitment into the CLSA.

Using a range of plausible response rates based on the pilot work completed by the CLSA, Figure 5.2 delineates the anticipated recruitment of participants from the CCHS Healthy Aging into the CLSA Tracking.

#### *5.2.4. Supplementing the CCHS Healthy Aging Sample for the CLSA Tracking and Comprehensive*

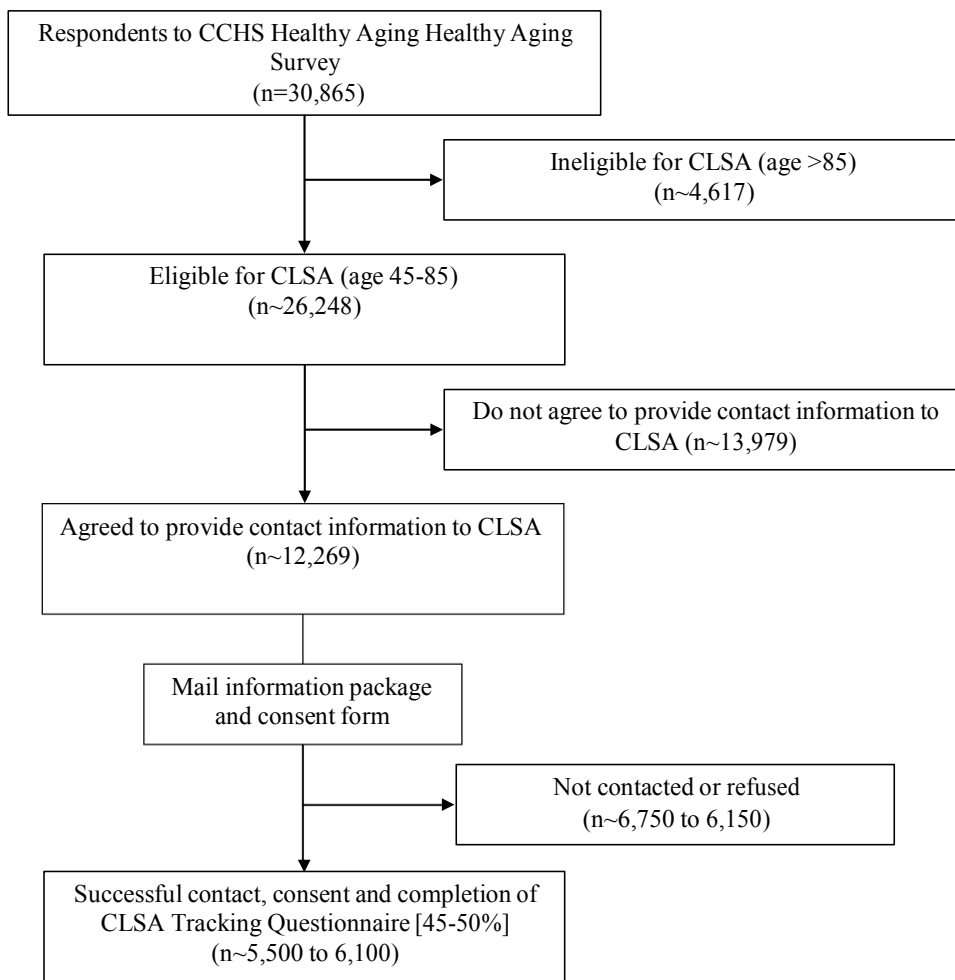
Our pilot work indicated that we would be able to recruit almost a third of our required CLSA Tracking cohort from the CCHS Healthy Aging (see Figure 5.2). Because some of the CCHS participants who provided their contact information to the CLSA were not actually eligible for the CLSA (due to language or cognition issues [CLSA only includes participants who can be interviewed in English or French and do not require proxy interviews at baseline]), the number of recruits from this sampling frame was lower than anticipated. In practice, we were able to recruit approximately 5,000 of the 20,000 tracking participants via CCHS. To obtain the full complement of CLSA Tracking participants we revisited the options of using additional Statistics Canada surveys (e.g. CCHS 5.1), provincial healthcare registration databases, random digit dialling, or using a private marketing company's telephone sampling frame (e.g., Léger Marketing).

The first option we considered was to collaborate again with Statistics Canada to augment the sample using the next CCHS survey as a recruitment vehicle. As described earlier, the CCHS consists of two cross-sectional surveys conducted over a two-year period in a repeating cycle. In the first year of each cycle (x.1), the goal is to provide estimates at the level of 136 regions, and the sample size is in the order of 130,000. In the second year of the cycle (x.2), the data are collected to provide estimates at the provincial level, with a correspondingly reduced sample size (n~30,000). The next scheduled CCHS survey was conducted in 2009-2010. However, this survey was not conducted using face-to-face interviews which would make obtaining signed consent to share contact information from CCHS participants much less practical and more costly. Thus, this option was discarded.

The preferable option to supplement the CLSA Tracking sample was to utilize provincial healthcare registration databases. Like the CCHS, this option would allow us to compare responders and non-responders on key demographic variables. As well, it would optimize resources and achieve economies of scale because these databases would be used to recruit the sample for the CLSA Comprehensive as well as the Tracking.

The option of using provincial healthcare registration databases as a sampling frame for the remainder of the CLSA Tracking and for the CLSA Comprehensive built upon extensive pilot work that was conducted to learn about province-specific data liberation regulations.(268) Because each province has a unique set of data liberation requirements, it was concluded that it was not possible to use health registration databases for recruitment in all provinces in the timeframe required for CLSA recruitment.

**Figure 5.2 – Anticipated Recruitment of Participants from Statistics Canada CCHS Healthy Aging into the CLSA Tracking**



#### 5.2.4.1 *Sampling from Provincial Healthcare Registration Databases*

The sampling strategy used by Statistics Canada for the CCHS Healthy Aging was built upon to select additional participants to achieve the desired sample size of 20,000 for CLSA Tracking. Because CATI interviewing is used in the CLSA Tracking, there was no need for cluster sampling as done for the CCHS face-to-face interviews, and so stratified random sampling was used to choose potential participants.

Within each province, a minimum number of participants for each age/sex category was required to provide minimum precision ( $n=125$ ). The remaining sample was divided among the provinces based on their relative population size using power allocation. Within the province, the additional sample (beyond the minimum required for each age/sex category) was allocated to meet our overall age-sex distribution (see figure 5.1).

Because the structure of the health registration databases varied by province, the CLSA researchers specified the age-sex distribution of the sample required from each province and worked with the data stewards to operationalize the selection.

The recruitment projections from Provincial Healthcare Registration Databases into the CLSA Tracking and Comprehensive were based on the Canadian Study on Health and Aging (Figures 5.3 and 5.4). The CSHA, however, recruited participants Canada-wide in the early 1990s. It is well recognized that response rates for population-based studies have been on the decline (275), and it was thus anticipated that additional methods of recruitment would be required. In practice, although the rates varied by province, age and sex, the proportion of people agreeing to allow CLSA to contact them range from about 6% to 25%; considerably less than the 50% experienced by the CSHA.

As recruitment through Provincial Health Registration databases is very resource intensive (for the Provinces and the CLSA), it was decided to use random digit dialling as a third sampling frame to supplement the recruitment of participants into the CLSA. While recruitment through Provincial Health Registration databases required large mail-outs of invitations to potential participants of the CLSA, random digit dialling had the advantage that provincial sampling age-sex quotas could be managed more precisely and the sampling strategy could be adapted over time to ensure all quotas are filled.

It should be noted, however, that we excluded cell phones from our RDD sampling frame. There are ethical issues with contacting people via cell phones due to potential costs incurred by respondents and potential safety issues as the mobile nature of cell phones allows for a respondent to be engaged in numerous activities such as the operation of a motor vehicle. In fact, in the United States, one must obtain prior express consent before contacting a person on a cell phone using an automatic telephone dialling system.(276) Consequently we explicitly excluded “cell-phone only” households from our sampling frame. We anticipate that this additional exclusion criterion will have only a modest impact in our target population. In 2010 Statistics Canada reported in their Residential Telephone Service Survey that in households with adults age 35 years and older, approximately 8% used a cell phone exclusively; the figure was 4% for people 55 years and older. In our population of men and women 45-85 years old at baseline we anticipate that approximately, 5% will not be included in our sampling frame due to exclusive use of a cell phone.

#### *5.2.4.2 Sampling using Random Digit Dialing*

A pilot study was conducted to examine the feasibility of recruiting potential participants for both the Tracking and Comprehensive cohorts using RDD. For the Tracking cohort, RDD was used to pilot-recruit 150 English-speaking residents and 150 French-speaking residents aged 45-85 for a telephone-administered questionnaire. The sample was chosen to approximate the age-sex breakdown of the sample required in the CLSA Tracking cohort.

As a first step, potential participants were contacted and those who were both interested in the study and agreed to receive an information package (pilot pre-recruits) were sent study information. Once the information package was received, these pilot pre-recruits were re-contacted and asked to complete a telephone interview. Overall, 42,608 calls were required to identify 708 pilot pre-recruits who agreed to be sent study information. Of these, 300 (42.4%) became recruits, i.e., agreed to complete an interview.

Similar methods were then used to recruit approximately 50 English-speaking and 50 French-speaking participants for the interviewer-administered and physical assessment component of the CLSA Comprehensive pilot (i.e., to mimic participation in the Comprehensive cohort). The comprehensive pilot was conducted at the McMaster and McGill sites only. Recruits for the Comprehensive pilot were required to agree to both a face-to-face in-home interview and a 2-hour assessment at the McMaster or McGill DCS. Multiple calls were often required to reach a potential pre-recruit. A total of 12,267 calls were required to recruit 131 pilot pre-recruits of which 86 (66%) agreed to participate in an in-home interview and physical assessment.

Based on this pilot work, we engaged Leger Marketing to obtain the additional pre-recruits necessary to complete the recruitment of the CLSA participants.

To identify pre-recruits, a random sample of landline phone numbers was chosen in the selected geographic areas (within the 10 provinces for the Tracking and within a 25 km radius of a data collection site for the Comprehensive). For some numbers, we expected that it would not be known in advance if the number is a working number, a private residence, and/or geographically eligible. Eligibility on these criteria was established by Leger.

Each phone number was called in the order in which it was selected. If the number was out of order, that was recorded. If an answering machine was reached, a message was left. If there was no answer, up to 10 further attempts were made at different times and on different days of the week.

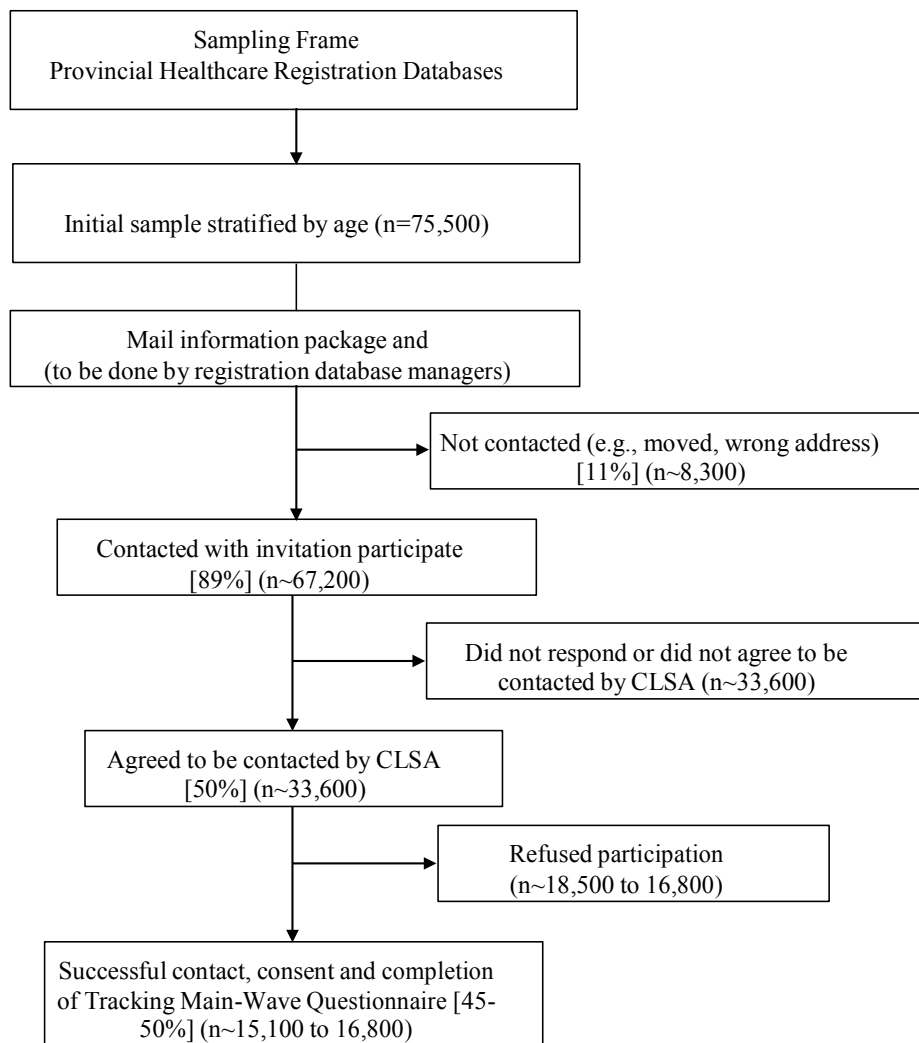
When the call was answered, eligibility was established (number is for a private residence, geographically eligible and age-eligible) A roster was made of all such household members. A random selection was made of one eligible household member, taking into account whether any of the age and sex quotas for the geographic area had been filled. The contact information for the identified pre-recruits was provided to CLSA weekly.

#### *5.2.5 Integrating samples from different sampling frames*

Sampling weights are needed to correct for imperfections in the sample that might lead to bias and other departures between the sample and the reference population. Such imperfections include the selection of units with unequal probabilities, non-coverage of the population, and non-response. Sampling weights

are determined such that the Tracking sub-samples from the three sampling frames and the Comprehensive sub-samples from the two sampling frames can be combined. The CLSA Methodology Working Group has responsibility for addressing the details of the sampling strategy and determining overall sampling weights.

**Figure 5.3 – Supplementing the Recruitment of CLSA Participants into the CLSA Tracking Using Provincial Healthcare Registration Databases<sup>1</sup>**



<sup>1</sup> Projected contact rate based on Canadian Study of Health and Aging: McDowell I, Aylesworth R, Stewart M, Hill G, Lindsay J. Study Sampling in the Canadian Study of Health and Aging. *Int Psychogeriatr* 2001;13(Supp 1):19-28.

### 5.3. Inclusion and Exclusion Criteria

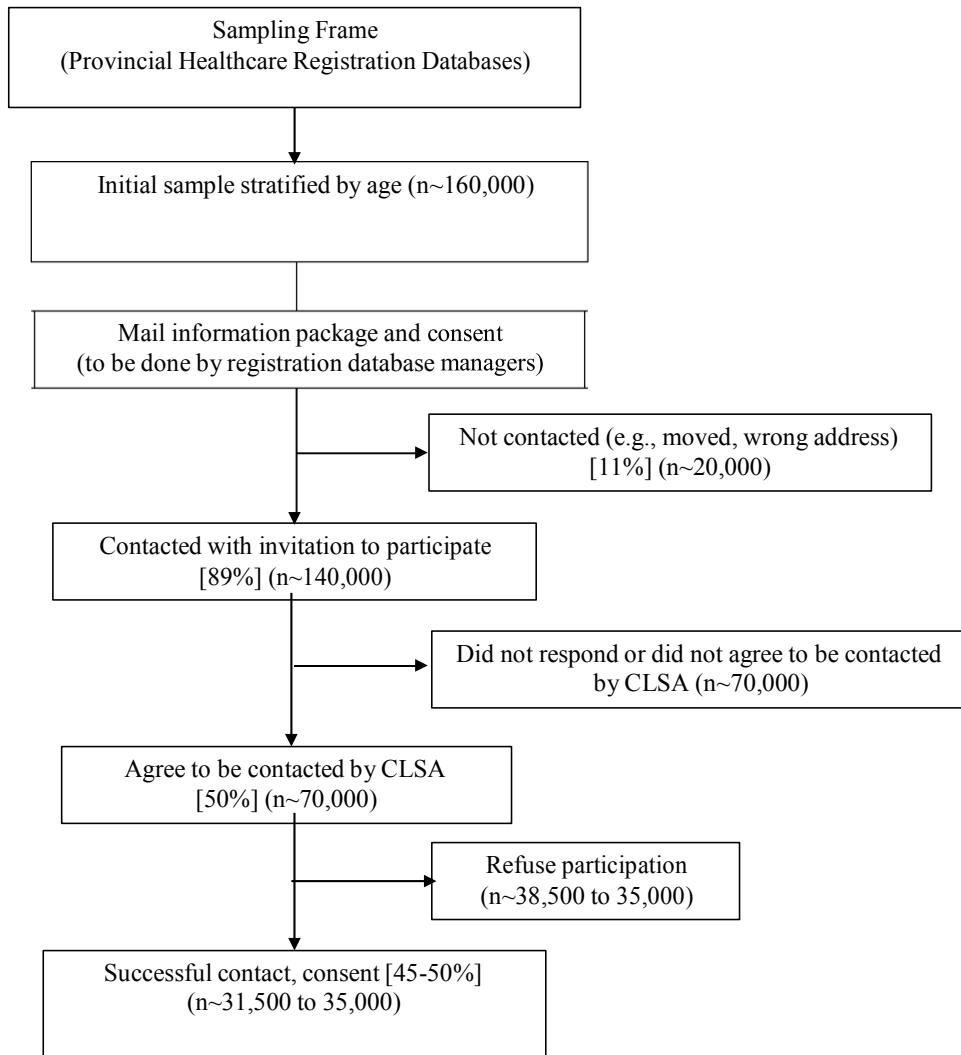
Since the CCHS was used to recruit participants into the CLSA Tracking, the selection of all 50,000 participants has been governed by the characteristics of the CCHS sampling frame. This facilitates the combination of common data among sampling frames and from the two cohorts.

The CCHS Healthy Aging sample is nationally representative (i.e., there is no over-sampling of less populous regions or special populations such as ethnic groups). Excluded from the sampling frame, and consequently the CLSA are residents in the three territories and some remote regions, persons living on federal First Nations reserves and other First Nations settlements in the provinces, full-time members of the Canadian Armed Forces, and individuals living in institutions. This latter exclusion means that individuals living in long-term care institutions (i.e., those providing 24-hour nursing care) are excluded from the CLSA at baseline. Individuals living in households and transitional housing arrangements (e.g., seniors' residences, in which only minimal care is provided) are included at baseline. As well, when sampling from Ministry health registration databases, we excluded people who were temporary visa holders or had transitional health coverage (when the information was available), as this represented a more transient population that may be difficult to follow in a long-term study. Participants who become institutionalized during the course of follow-up will remain in the CLSA and will continue to be followed through either personal interview or interviews with proxies. Participants who move within, between provinces, or from a province to a territory will also be followed at their new location if possible.

Individuals unable to respond in English or French are excluded from the CLSA. The presence of a chronic medical illness at baseline is not a reason for exclusion from the study. However, individuals with cognitive impairment at baseline are excluded. The presence of cognitive impairment not only potentially compromises the capacity to give informed consent, but may also affect the reliability and validity of interview responses. There are several methods to screen for cognitive impairment at the time of recruitment into the CLSA, including face-to-face assessment and telephone administered cognitive screens.<sup>(277)</sup> Given that some of our participants are recruited from the CCHS, we have chosen to follow the strategy used by Statistics Canada. Statistics Canada uses interviewers with extensive training and interviewing experience. CCHS interviewers are trained to identify individuals who are unable to understand the purpose of the survey and provide reliable data. Using a similar methodology, potential participants are excluded if CLSA interviewers judge them unable to understand the purpose of the study and/or provide reliable data. It is likely that the vast majority who are excluded in this way are cognitively impaired.

To participate in the CLSA Comprehensive, individuals must agree to participate in an in-home interview and to the collection of anthropometric, neuropsychological, and physical measures at the DCS. Comprehensive participants have the option of refusing to provide biological specimens.

**Figure 5.4 – Recruitment of CLSA Comprehensive Participants Using Provincial Healthcare Registration Databases<sup>2</sup>**



<sup>2</sup> Projected contact rate based on Canadian Study of Health and Aging: McDowell I, Aylesworth R, Stewart M, Hill G, Lindsay J. Study Sampling in the Canadian Study of Health and Aging. *Int Psychogeriatr* 2001;13(Supp 1):19-28.

#### **5.4. Special Populations**

The possibility of over-sampling special populations, including aboriginal and ethnic populations, was explored during the development of the CLSA, but was determined not to be a viable strategy at the study outset. Briefly, it was felt to be inappropriate to combine dissimilar ethnic groups and logistically too difficult to obtain sufficient sample sizes for adequate statistical power in distinct ethnic subgroups. Research studies in aboriginal populations must also be developed in collaboration with the Aboriginal community such that the objectives and content are relevant to them. It was decided for these reasons not to include special populations at baseline. In future, an aboriginal cohort that would complement the CLSA cohort might be established in cooperation with the aboriginal community. Information on individuals from special populations will, however, be captured to the extent that they are selected through the proposed sampling strategy.

#### **5.5. Preparing for Participant Recruitment into the CLSA**

In preparing for the CLSA, we conducted a pilot study involving six focus groups across Canada (43 participants total) and found generally positive attitudes toward participating in a longitudinal study like the CLSA.(278) The focus group participants believed the CLSA was an important and timely endeavour. They valued research on health and aging, and would consider participating in a study of this nature for altruistic reasons. They trusted university researchers to conduct the study, and felt that government was the appropriate funder.

Prior to going into the field, multiple communications strategies were implemented to encourage participation in the CLSA by outlining the importance and relevance of the study. A CLSA awareness campaign was launched in 2012 and included newspaper articles and interviews with CLSA researchers on radio and television. The CLSA also developed and used other platforms, such as its website and social media channels to engage potential participants. Previous research and the CLSA investigators' own prior experiences conducting both cross-sectional and longitudinal studies suggest that multiple, overlapping strategies are necessary to meet recruitment goals and that continual monitoring and adaptation of strategies is imperative.

#### **5.6. Process for Initial Contact with Potential Participants**

##### *5.6.1. CLSA Tracking*

For the CCHS sample, Statistics Canada staff were responsible for the initial participant contact, which occurred during the conduct of the CCHS Healthy Aging interview. Statistics Canada included two questions in the CCHS Healthy Aging regarding sharing participant information with the CLSA. Participants were asked to provide permission for Statistics Canada to: 1) share their CCHS Healthy Aging study data and 2) share their contact information with the CLSA. CCHS participants had the option of providing permission for both; for one or the other; or for neither. Once Statistics Canada obtained permission from potential participants to forward their personal coordinates (contact information) to the CLSA, all further contact and follow-up became the responsibility of the CLSA research team. The lead institution (McMaster) received the names from Statistics Canada in encrypted electronic files. After assigning unique numeric identifiers to each of the records and ensuring that the records are complete, the CLSA National Coordinating Centre (NCC) at McMaster distributed geographically grouped names to the four regional CATI sites.



The NCC mailed potential participants an information package that included an introductory letter, information about the study, and the study consent forms (see Appendix D). The package was submitted to the Ethical, Legal, and Social Issues (ELSI) Committee for review prior to its submission to the research ethics boards. The ELSI Committee falls under the jurisdiction of CIHR and was formed to provide ongoing advice regarding ethical, legal, and social challenges that may arise during the implementation and conduct of the CLSA.

Interviewers at the CATI sites contacted the potential participant by telephone within two weeks of the information package being sent. The CLSA CATI interviewer explained the study in detail, answered questions, and guided participants through the consent process (approximately 10 minutes). If oral consent was given, then the interviewer conducted a 20-minute interview, which was the Tracking Recruitment Questionnaire for CCHS Healthy Aging Participants.

The CCHS Healthy Aging questionnaire, which Statistics Canada developed in close collaboration with the CLSA, contained some content that was specific to the needs of Statistics Canada and other stakeholders, but was of lesser relevance to the CLSA. To keep within the timeframe of the CCHS interview, not all of the CLSA core content was included in the CCHS Healthy Aging survey. Thus, the 20-minute Tracking Recruitment Questionnaire for CCHS Healthy Aging Participants collected the additional CLSA core content. The script for the initial CLSA contact is in Appendix E1.

A similar process was undertaken for the remainder of the Tracking participants recruited through health registration databases. The NCC prepared a similar information package including an introductory letter, information about the study, and the consent to contact form. However, for this group, the provincial government departments or data stewards responsible for housing the healthcare administration databases mailed the information packages directly to the randomly chosen persons on behalf of the CLSA.

Depending on provincial requirements, the introductory letter included in the information package was signed either jointly by a provincial government representative designated by the province in question and the lead PI for the CLSA, or separate introductory letters from the CLSA and/or Ministry were included. The letter clearly indicated that the package was being mailed by the government on behalf of the CLSA, and that the CLSA did not have access to any identifying information. Potential participants were invited to contact the CLSA (via a 1-800 telephone number, the website, or by mail [letter or electronic]) to hear more about the study and indicated their willingness to be contacted by a member of the CLSA team. Only those who mail back their contact information to the NCC were be contacted.

For the RDD pre-recruits, Leger was given scripts developed by the CLSA investigators to introduce potential participants to the study (Appendix E). After describing the study and establishing eligibility, an interested “pre-recruit” was asked to provide their name, address, phone number and preferred day of the week and time for telephone contact to the operator. Leger provided contact information for pre-recruits weekly using encrypted electronic files. The files are uploaded by the NCC and an introductory letter, information package and consent form were mailed to the pre-recruit prior to being contacted by the CLSA for a recruitment interview.

The process of contact by the CLSA was the same for those recruited through provincial health registration databases and RDD as for those recruited through the CCHS except for the length of the

recruitment interview. Because the non-CCHS recruits did not have the supplemental CCHS data, those participants recruited through the Health Registration Databases and RDD were guided through the consent process (approximately 10 minutes) and complete the full 60-minute Tracking Main-wave Questionnaire.

About 18 months after their initial CCHS Healthy Aging interview, the CCHS-recruited participants also completed the full 60-minute Tracking Main-Wave Questionnaire. The 60-minute Tracking Main-Wave Questionnaire is considered the baseline interview for all 20,000 Tracking participants.

All potential participants were contacted by CATI interviewers. CATI staff work in staggered shifts to permit calls between 8:00 and 20:00 local time throughout the week. Up to ten attempts are made to contact each potential participant. Based on findings from the pilot study, the interviewer leaves a short message if the call is unanswered. If the participant is reached yet is unable to complete the interview at the time of the introductory phone call, then the interviewer schedules another time to conduct the interview. As part of the interview, the study candidate's written consent is sought for their agreement to be contacted again as part of the longitudinal component of the CLSA, as well as for the linking of their questionnaire data to data retrieved from provincial healthcare registration databases (e.g., physician claims data, hospital discharge abstracts). Participants are asked to provide their health insurance number (HIN) during the interview to allow for data retrieval and linkage. Participant refusal to provide their HIN does not exclude them from the study if they have agreed to longitudinal participation. All participants are also asked to provide the name and contact information of at least one alternate contact person who would be aware of their whereabouts if they move. Participants who are 70 years or older at the time of a main-wave interview are also asked for contact information for: 1) a legally-appointed person or other person who could make decisions for them if they were no longer able to make decisions in the future (a "proxy"), and 2) a person who knows them well or sees them frequently that could answer questions on their behalf if they are unable to participate in a CLSA follow-up interview (an "informant"). These two roles may be held by the same person or by two different people. Participants are advised that they may withdraw from the study at any time and they are provided with the information needed to do this. The CLSA withdrawal scripts are in Appendix E.

To participate in the CLSA Tracking, a signed consent form must be returned to the NCC by mail. Participants are advised of this requirement during their interview. The NCC informs the CATI sites once written consent has been obtained. If the signed consent form is not received, the NCC sends another consent form and the participant is re-contacted to remind them that a written consent form is required for participation in the CLSA. If consent is not obtained after two reminders, the participant is informed by mail that they are removed as a participant in the CLSA study.

Each CATI site is responsible for contacting potential participants and interviewing them. The NCC and CATI staff work together to re-contact participants if needed to ensure the return of the signed consent forms. The CATI sites maintain a record of contact (ROC) to track the results of all call attempts. In addition, CATI sites have implemented specified protocols to assure data accuracy, integrity, and security. (See section 6.2).

#### *5.6.2. CLSA Comprehensive*

The NCC also prepares an information package for all potential CLSA Comprehensive participants. The package includes an introductory letter, information about the study, and the study consent forms (see

Appendix D). The package is similar to the package used in the CLSA Tracking, although it contains additional information about the DCS visit and biospecimens collection. The package was submitted to the ELSI Committee for review prior to submission to the CLSA site research ethics boards.

The process of initial contact, through either health registration databases or RDD, is essentially the same for the Comprehensive as the Tracking. The only difference is the geographical restriction of the Comprehensive participants to within 25 km of the DCS. For both methods of recruitment, a set of “acceptable” postal codes were provided to identify the geographic area for recruitment. Data stewards restricted their sample to this area and Leger asked an additional screening question related to potential participant’s postal codes.

Similar to the Tracking, the NCC is responsible for distributing pre-recruit contact information to the data collection sites for the comprehensive. The DCS makes the initial contact with the potential participant to verify that they meet the inclusion criteria, to answer questions about participating in the study, to affirm the person’s interest to participate in the CLSA. If the pre-recruit is interested, the DCS arranges a convenient time for a home interview.

DCS staff work in shifts to permit calls between 8:00 and 20:00 local time Monday through Saturday. Up to ten attempts are made to call each potential participant. A brief message is left on answering machines if the call is unanswered. If the participant is reached, but is unable to speak with the interviewer at that time, then the interviewer schedules another time to talk. Telephone contact scripts are contained in Appendix E.

### **5.7. Informed Consent**

The information and consent packages for the CLSA Tracking and Comprehensive are written in lay language and outline the purpose and the nature of study, the study methods, and the requirements for participating in the study, and the anticipated risks and benefits. In these packages, potential participants are informed that their participation is voluntary, that they have the right to withdraw from the study at any time, and that any decision to participate will not affect their access to health or social services. The packages also explain that all data will be kept confidential, research will be conducted in accordance with the legal and ethical standards used for medical research, and data will never be used to identify individuals in research reports.

Because the CLSA will be an important platform for future research, many analyses that will be conducted cannot be specified at the time of recruitment. Participants are told that continued contact with CLSA researchers over the duration of the study will be useful to provide data that meet the needs of evolving science. Participants will be asked to confirm or reconsider their participation in the CLSA at each follow-up contact. Finally, participants are informed that independent committees will monitor the conduct of the study and will ensure that the interests of the participants and public in general are served by the study. The Advisory Committee on ELSI for the CLSA (see section 10 Governance and Study Management) and Research Ethics Boards act in this capacity.

### **5.8. Timing of Follow-up**

The schedule of follow-up assessments and interim contacts is identical for both the CLSA Tracking and Comprehensive components of the CLSA. The CLSA will conduct a wave of primary data collection on all CLSA participants every three years. These primary data collection waves will be supplemented by a

brief, mid-wave, telephone interview to maintain contact and sustain ongoing relationships between CLSA staff and participants. This mid-wave data collection, referred to as the Maintaining Contact (MC) Questionnaire (separate questionnaires for the Tracking and Comprehensive components of the CLSA), is an important strategy in a longitudinal study and will not only enhance the ongoing relationship between study participants and the CLSA team, but will also allow us to update contact information for the participants more easily than if we wait for three full years to re-contact. Finally, the MC Questionnaire will permit the collection of a limited amount of additional questionnaire data. The MC Questionnaire will be conducted using CATI for both Tracking and Comprehensive and will take approximately 30 minutes.

Each individual will be followed for at least 20 years or until death. Participants will be considered as censored if they are lost to follow-up, refuse continued participation, or are still alive at the end of the study period. Repeated follow-ups allow the CLSA to obtain data on changes over time. For example, participants who visit a DCS undergo performance testing (i.e., grip strength, timed-up-and-go, chair rise, four-metre walk test) at three-year intervals. This will provide data on how physical performance changes over time. As well, by linking physical performance to other variables (e.g., measures of cognition or chronic disease), researchers can examine how physical performance affects, or is affected by, other participant characteristics over the course of the study.

Repeated follow-ups will also allow researchers to estimate the incidence of disease or health conditions over time. This will be especially beneficial for conditions such as parkinsonism, where no reliable measure of incidence exists for the Canadian population.(150)

The longitudinal design of the CLSA also permits the investigators to supplement existing data collection with new questions or tests in the future. These new questions or tests might be added to enable researchers to measure something for the first time (e.g., a blood test to screen for Alzheimer's disease) or to measure newly discovered diseases.

### **5.9. Cognitively-impaired Participants and Proxies**

At recruitment, trained interviewers identify individuals who are unable to provide informed consent or who are judged unable to provide reliable information. These individuals are excluded from participation. This is the same procedure used by Statistics Canada in the CCHS.

During the course of the CLSA, however, it is likely that some older participants will develop cognitive decline, which will preclude them from completing all or part of their interviews. Since the prevalence and incidence of cognitive impairment increases with age, but is relatively rare amongst individuals under the age of 70, we have chosen this age as the cutpoint to initiate inquiry regarding a proxy protocol. Thus, participants who are 70 years and older are asked how they would like to participate in the CLSA in the future in the event of cognitive decline or if they are unable to participate on their own for other reasons.

In terms of cognitive decline, two issues arise: the first is the ability to make decisions concerning continuing participation in the study; the second is the ability to participate (i.e. answering questions, performing tests). If they indicate that they would like to continue participating in the CLSA when they are not able to provide continuing consent participants are asked to provide the name and contact information of a person who can make decisions on their behalf (i.e. a proxy decision maker). This

person (the proxy) may be the same person who the participant would designate as the person who would respond on their behalf to some of the questions posed as part of the CLSA (i.e. an informant). If a participant chooses not to identify a proxy and/or informant, it will not affect their inclusion into the study. Consent from the proxy and/or informant will be obtained only when the need for a proxy is identified. It is understood that the requirements for a proxy for research purposes may differ by province. We have consulted with our Ethical, Legal and Social Issues committee to identify any potential issues. The proxy and informant information packages and consent forms are included in Appendix D.

In subsequent waves, participants who have identified a proxy and/or an informant will be asked to reconfirm the person(s) they have chosen and the contact information. At each main-wave interview, participants who have turned 70 since the last CLSA wave will be asked how they would like to participate in the CLSA in event of cognitive decline and to undertake the proxy consent to contact process.

As noted above, one of the major reasons for being unable to participate in subsequent data collection is likely to be a decline in cognitive abilities. It would be a great advantage if we were able to identify individuals at highest risk of cognitive decline during the course of the CLSA so that we might be able to predict those participants for whom we may need to collect data fully or in part through an informant and/or for whom we may need to contact a proxy decision maker. Part of the background to the development of this identification strategy will be analyses conducted on the neuropsychological tests collected at the CLSA baseline. As part of a validation study done in collaboration with Statistics Canada, norms were established for both French and English versions of the short battery used in the CLSA Tracking. Participants in the CLSA Comprehensive will undergo their neuropsychological testing at a DCS. This neuropsychological battery includes the “short” battery that will be administered to the participants in the CLSA Tracking over the phone. Following the CLSA Comprehensive baseline data collection, analyses will be conducted within the data from the CLSA Comprehensive cohort to examine whether the use of the short battery alone could serve as a predictor of performance on the longer DCS-administered neuropsychological battery. These tests will be supplemented with self-reported information about whether the individual has been told by a doctor that they have memory problems and whether they have been told by a doctor that they have dementia or Alzheimer’s disease. Together these sources of information will allow us to screen for cognitive deficits that may make it difficult for the participant to provide reliable responses and will be triangulated with interviewer judgement of the individual's ability to understand the study. In the event that a person is considered unable to adequately respond, or deems themselves unable to respond, they will be informed that the proxy and informant will be contacted.

#### **5.10. Harmonization of data collection**

Although the sampling strategy for the CLSA Comprehensive and the CLSA Tracking cohorts differ, these two components share core content measuring physical functioning, psychological functioning, and social functioning (see Appendix B and C). The mode of data collection for the two CLSA components during follow up also differs, as does the scope of the information being collected. Nevertheless, sampling methods and core measurement tools have been harmonized between the CLSA Tracking and Comprehensive components of the CLSA to be able to use all 50,000 participants for key analyses. Furthermore, the CLSA has utilized, wherever possible, questionnaire modules that can be harmonized with questionnaires used by other national and international cohorts (e.g. the Health and

Retirement Study, the Canadian Partnership for Tomorrow project), which will allow for even broader retrospective and prospective harmonization of the CLSA cohort data.

### **5.11. Response Rates**

In a study of this magnitude, the proportion of eligible subjects contacted who agree to participate is of concern. Non-response or refusal to participate can result in selection bias if those who agree to participate differ in some systematic way from those who do not. Apart from individuals who refuse outright to participate, some will initially agree to participate only to refuse later when contacted by CLSA interviewers. In addition to refusals, some eligible subjects will be unable to be contacted, due to incorrect contact details either because they have moved since participation in the CCHS, or if their new address is not updated in the health registration databases or because after repeated efforts, contact cannot be made.

To be confident of obtaining the target sample size, it is important to consider response rates when estimating the number of individuals who need to be contacted. We have used published information from other large-scale studies in Canada and elsewhere as a guide to obtaining the target sample size. In the 2000 Canadian Community Health Survey, the average national response rate was nearly 85% after 14 months of collection.(272) The longitudinal component of the National Population Health Survey reports response rates in the same magnitude; the U.S. Health and Retirement Survey reports response rates of 80-82%.(279) These latter studies are all questionnaire-based. However, population-based longitudinal studies that require clinical assessments report lower response rates. For example, in the Canadian Multicentre Osteoporosis Study (CaMos), which included participants aged 25 years and older who were recruited using telephone lists, overall response rates were in the order of 46%, though response rates were higher in the older age groups.(280) In the CSHA, which included participants aged 65 years and over, the response rate among those contacted was 72%.(281) However, the denominator used to calculate this figure included a large number of people in the sampling frame whose contact information was outdated on the health insurance lists and could not be contacted. Of those contacted by the CSHA interviewers, the response rate was over 80%. Response rates varied widely across the country, with lower rates in larger cities. It is also well recognized, however, that response rates for population-based studies have been on the decline.(275). Our experience to date indicates that the response rates from different modes of recruitment have been lower than anticipated.

Preliminary data also suggest that response rates differ between the Comprehensive CLSA and the Tracking CLSA. This is likely due to the differing intensity of participation required. Concerted efforts such as repeat contact call procedures have been put in place to ensure optimal response rates in the CLSA. Use of weighting and non-response adjustment will be made to compensate for these factors in the analysis.

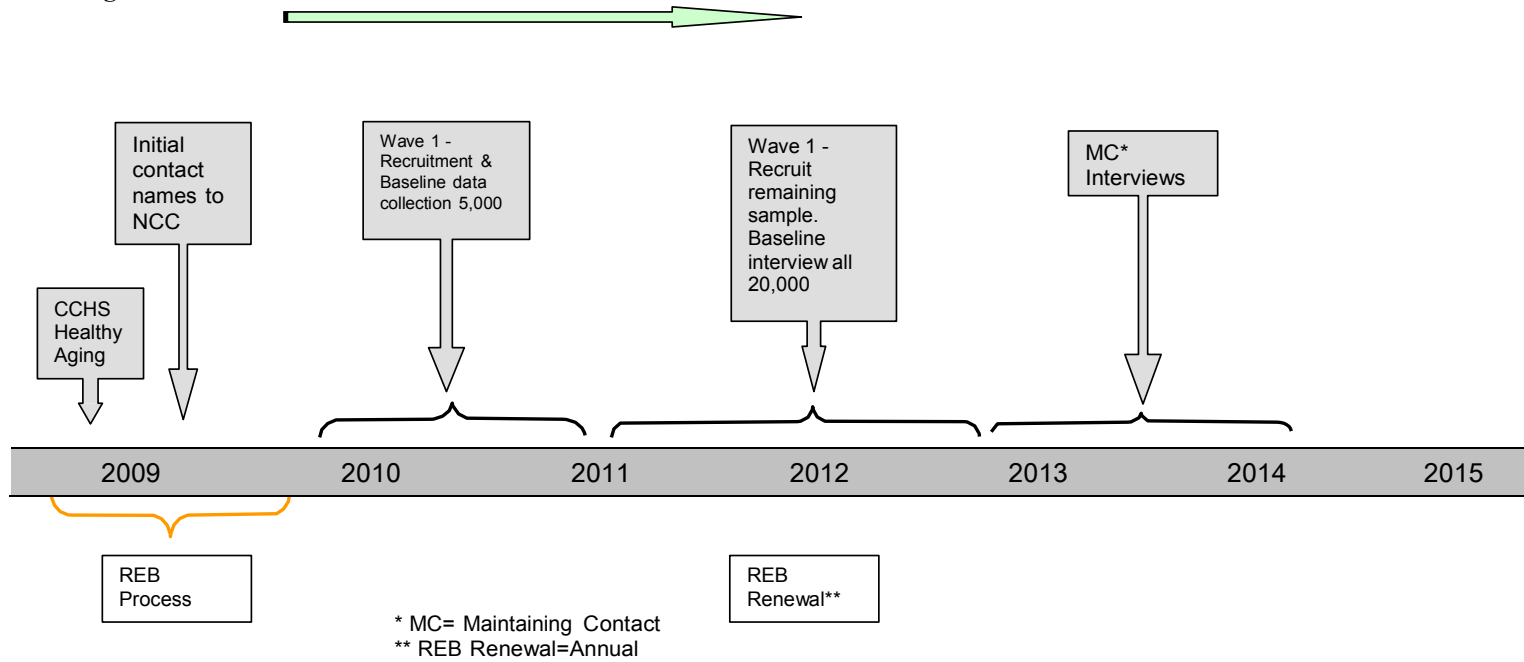
### **5.12. Recruitment Timelines**

Recruitment into the CLSA Tracking is staggered over two years. The first group was recruited from the CCHS Healthy Aging participants in 2010. The supplemental group (to complete the cohort of 20,000) were recruited and interviewed in 2011-2013. Staggered recruitment allows us to rollout the infrastructure and the personnel needed to run such a large study. It also allowed us to assess the age, sex, and geographical distribution of our CCHS-based sample prior to selecting the supplemental sample. If the sample is not proportionally representative of the regions across Canada, specific groups or regions can be over-sampled or under-sampled in the supplemental group to attain a more

proportionally representative sample. We anticipate the completion of baseline (first wave) data collection on all 20,000 CLSA Tracking participants in early 2013, completion of the first set of MC Questionnaires on all 20,000 by mid-2014, and completion of the second wave of data collection on all 20,000 by early 2016 (see Figure 5.5).

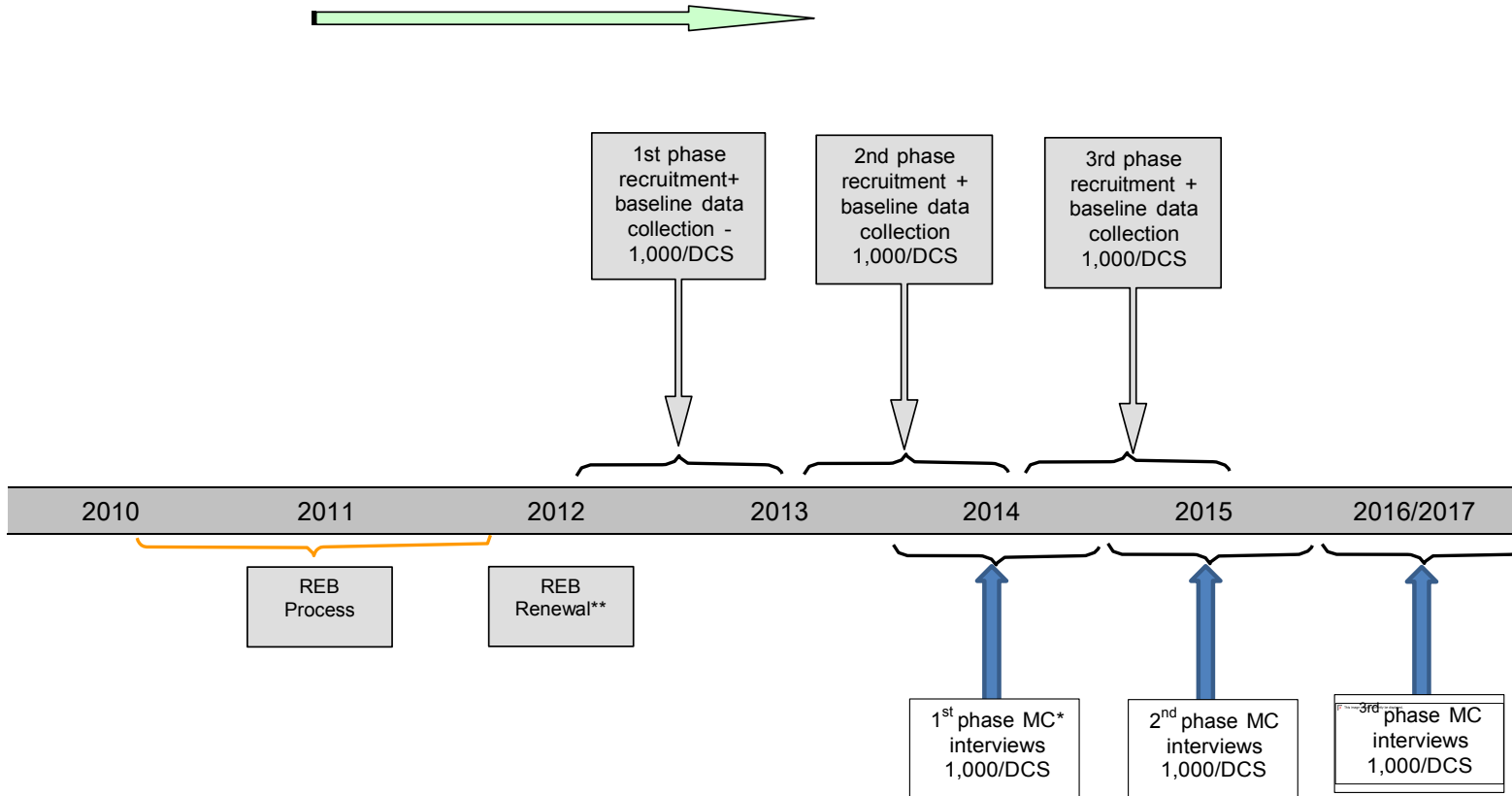
Recruitment into the CLSA Comprehensive is also staggered over time to accommodate data collection. First-phase recruitment commenced in mid-2012 and will last for one year. Subsequent recruitment phases will run mid-2013 to mid-2014 and mid-2014 to mid-2015. During each phase, 1,000 persons will be recruited per DCS, for a total of 10,000 participants per year. Thus, by mid-2015, all 30,000 participants will be recruited into the CLSA Comprehensive and the (baseline) first wave of data collection will be complete. Each participant's first MC Questionnaire interview will take place approximately 18 months following baseline data collection, so the first set of MC Questionnaire interviews will be completed by the early 2017 (See Figure 5.6).

**Figure 5.5 Tracking Cohort Timeline**  
**Tracking Cohort**





**Figure 5.6 Comprehensive Timeline  
Comprehensive Cohort**



\*MC = Maintaining  
Contact  
\*\* REB  
Renewal=Annual

### **5.13 Assessing representativeness and potential selection bias**

As with many population-based studies(275), the response rate for the CLSA is lower than anticipated compared to those reported in prior Canadian population-based studies, such as the CSHA. Having a lower response rate increases the risk of selection bias and reduces the likelihood of having a representative sample.

We were able to examine this issue, in part, in the 2009 CLSA pilot. The pilot encompassed 596 persons who were recruited from the CCHS Healthy Aging Pilot Study. There were very few differences between responders to the CLSA pilot questionnaire and non-responders. Although as is seen in many studies, the responders were slightly more educated than the non-responders.

Since our main sampling frame for the CLSA Tracking is the CCHS Healthy Aging, we are also able to use aggregate data from the CCHS to compare demographic characteristics, such as sex, age, socio-economic status, and health variables for those who agreed to share their contact information with the CLSA and those who did not.

The use of provincial healthcare registration databases as the sampling frame also allows us to compare responders and non-responders using aggregate-level demographic data retrieved from these databases (where available).

For the RDD-recruited sub-samples as well as the overall samples, we will also use census data to compare demographic characteristics. Census data for the population living within a 25-kilometre radius of each DCS will be used as the comparator against the sample characteristics of the Comprehensive participants who are recruited into the study.

Such comparisons will shed light on the underlying characteristics of potential selection bias and will support the development of corrective strategies to mitigate the impact of these factors on statistical analyses.(282;283) In the event of non-representativeness, the CLSA methodology group will explore methods to use data from other population-based studies, such as the Canadian Community Health Survey Annual Component (which is designed to provide reliable estimates at the level of the health region) as an auxiliary dataset to create corrected prevalence estimates from the CLSA data.

Although these methods of weighting can be used to help correct for non-representativeness, if there are insufficient numbers in some specific categories of data due to non-response (e.g., participants with lower education levels) it will limit the type of analyses that can be conducted and produce less precise estimates of effect. The CLSA principal investigators in collaboration with the methodology working group will work together to determine whether or not additional supplemental targeted sampling is required to ensure sufficient heterogeneity in factors such as education.

### **5.14. Participant Retention**

Once participants have enrolled in the CLSA, several approaches will be used to enhance participant retention. These approaches have been successfully used in other longitudinal studies such as CaMos(284) and the CSHA.(281) The approaches are:

- Regular updates to provide feedback and general study findings to participants;
- Inter-wave maintaining contact interviews (see section 5.8);
- A user-friendly website with information on the study written to be accessible to the lay public;

- Media coverage of the study to publicize the importance of CLSA research for Canadians;
- Public outreach and community engagement events, such as open houses and Café Scientifique events;

Other approaches may include CLSA merchandise (e.g. reminder magnets, pens and stationary), birthday cards and holiday season greetings in December each year, and the use of a CLSA membership card detailing the number of years of participation in the study as follows: bronze [0-5 years], silver [6-10 years], gold [11-15 years], platinum [16-20 years]. Another option may be to identify 'CLSA Champions' who consent to sharing their personal story about participation in the CLSA newsletter or on the CLSA website. All of these approaches will be evaluated for feasibility and effectiveness.

As part of our Maintaining Contact Interview, we will collect information on the type of communication tools (e.g. email, websites, social media, etc.) that participants use. We will utilize this information to tailor our communication strategies to the individual participants.

#### **5.15. Attrition Due to Deaths, Refusals to Continue, Losses to Follow-up**

Sample attrition due to losses to follow-up, deaths, and refusals to continue in the study will be an ongoing important challenge for the CLSA. Information provided by Statistics Canada on the attrition rates for the National Population Health Survey for the period 1994-95 to 2000-2001 (i.e., cycle 1 to cycle 4) provide the basis for an estimate of the proportion of study participants lost over the period. Based on the assumptions on mortality and attrition for age- and sex-specific groups over the duration of the study, roughly half of the sample will remain at the end of 20 years.

We will use several strategies to minimize losses to follow-up. A protocol for tracing study participants who are not located at follow-up will cover linkages with mortality databases and contact with alternate contacts identified at baseline. At each follow-up, some CLSA participants will have died, and we will make every effort to avoid upsetting family members with uninformed calls.

#### **5.16. Sample Size**

Estimation of sample size requires information on the specific effect sizes that are desired to be detected. Given the diversity of goals and statistical models that are bound to accompany them, it is virtually impossible to provide global meaningful effect sizes for sample size calculations. In addition, the use of the CLSA as a platform for future (and as yet unknown) research questions precludes such calculations. Consequently, one strategy we used is to carry out simulations based on simplified hypothesized evolutions of the cohort experience over time. Currently, the target sample size is 30,000 for the CLSA Comprehensive and 20,000 for the CLSA Tracking. The prevalence of selected exposures and the incidence of selected outcomes, such as particular chronic diseases, over the period of follow-up, were used as a guide to assess the *adequacy* of the proposed sample size.

First, the expected number of cases of an outcome was simulated for each 3-year wave of the CLSA based on sex- and age-specific incidence rates and taking into account the aging of the cohort over time.(285) To provide more realistic estimates the simulations also accounted for mortality (based on age and sex specific annual mortality rates from Statistics Canada) and attrition due to loss to follow-up (estimated at 0.5% per year based on the attrition rates for the National Population Health Survey (NPHS) for the period 1994-1995 to 2000-2001.(286) For a condition with a high annual incidence rate, such as hypertension (sex- and age-specific incidence rates ranging from 31 to 43 cases/1000 persons

per year)(287), we would expect almost 1,520 cases from a cohort of 20,000 people and between 1,860 and 2,580 cases from a cohort of 30,000 people (at the end of baseline data collection).

We also investigated power profiles for the CLSA for two types of outcomes: hazard ratio (for incidence studies) and an odds ratio (for nested case-control studies) based on an iterative simulation-based approach. Simulations were undertaken to determine the minimum detectable hazard ratio (MDHR) for the comprehensive cohort (n=30,000) and for the minimal detectable odds ratio (MDOR) for the combined cohort (n=50,000).

The irreversible time illness-death model, which is a commonly used multistage model (MSM) was adopted to capture the dynamics of change of participants' health conditions. In this model, participants' health states as assessed at each wave can be classified simply as 'Healthy', 'Diseased', or 'Dead'. Among these three states, 'Healthy' and 'Diseased' are transient states and 'Dead' is an absorbing state.

#### *Minimum Detectable Hazard Ratio(MDHR)*

To estimate the MDHR between an outcome (development of disease or death) and a risk factor a simulation study was conducted assuming a power of 80% for three disease outcomes: diabetes, dementia, and Parkinson's disease. These diseases were chosen because they represent different rates of progression, relatively quick (diabetes), relatively slow (dementia) and very slow (Parkinson's disease) as well as different prevalence's (about 0.14 for diabetes and 0.02 for dementia and Parkinson's disease). We also considered two types of risk factors: an environmental risk factor and a genotype risk factor, and their interaction. Risk factor prevalence (1%, 10%, and 20%) was considered in the simulation to represent a plausible range of exposure prevalence from very rare risk factors (1%) to common risk factors (20%). The simulation accounted for potential non-differential misclassification of both types of risk factors (10% for the environmental risk factor and 1% for the genotype risk factor. The simulation was based on the assumption that the diseases are not curable, i.e. transition from 'Diseased' to 'Healthy' cannot occur, and the transition times from state to state (i.e., healthy, diseased, dead) follow a Weibull distribution with a shape parameter greater than one (to capture the increasing hazard of state transition over time as one ages).

Under these scenarios the MDHRs for environmental with high prevalence ( $\geq 0.1$ ), the CLSA has sufficient power to detect small ( $1 < \text{MDHR} \leq 1.5$ ) to moderate ( $1.5 < \text{MDHR} \leq 2.0$ ) hazard ratios for diseases that have either fast or slow progression rates. For environmental risk factors with very low prevalence ( $\leq 0.01$ ), the CLSA only has sufficient power to detect moderate ( $1.5 < \text{MDHR} \leq 2.0$ ) to large ( $2.0 < \text{MDHR} \leq 3.0$ ) when risk factors are measured precisely. For genotype risk factors, the CLSA is capable of detecting moderate HR if the prevalence of the risk factor is high. The largest MDHRs ( $\text{MDHR} > 3.0$ ) were for interactions between environmental and genotype risk factors when the outcome and risk factors had low prevalence, and the progression speed for transitions was moderate or slow. Misclassification of exposure of 10% increased the MDHR substantially. Appendix F1 contains the power curves for different scenarios and a summary table of MDHRs.

#### *Minimum Detectable Odds Ratio(MDOR)*

We also conducted a similar set of simulation-based sample size calculations for nested case-control studies using the approach developed by Paul Burton(288) and used for the UK Biobank (Appendix F2). These simulations used logistic regression and took into account potential misclassification of both the risk factor and outcome. We again assumed a misclassification rate of 5% for the risk factor. For the outcome we assumed a 1% misclassification rate for those with disease and 10% misclassification rate for those without disease (i.e., sensitivity=99% and specificity=90%).

While the CLSA will not be powered to assess relatively rare outcomes, more common conditions and events will be feasible to detect in a nested case-control study. We calculated minimum detectable odds ratios (MDORs), based on 80% power and a two-sided alpha of 0.05. For a relatively common disease, such as diabetes mellitus, we anticipate that there will be approximately 3,200 incident cases by the end of the second wave of the CLSA. For a common disease such as this, in which we would identify 3,000 incident cases, MDOR for low prevalence risk factor ( $prev=0.05$ ) is 1.45 and for high prevalence risk factor ( $prev=0.5$ ) is 1.19. These MDORs assume no misclassification. The estimated MDORs are increased to 1.92 and 1.23 when one assumes misclassification of both exposure and outcome. The MDORs for a lower incidence disease for which 1,000 cases are identified are 2.71 (low prevalence risk factor) and 1.52 (high prevalence risk factor) assuming no misclassification. The MDORs are 3.59 and 1.46 when misclassification is taken into account. A summary of MDOR tables and power curves are included in Appendix F2. The use of continuous outcome measures (e.g., quantitative traits such as cognition) will result in greater statistical power to detect clinically meaningful effects.

### 5.17. Statistical Analysis

The core analyses of the CLSA data will be able to inform cross-sectional and longitudinal research questions. After the first wave of data collection, we will have data on the prevalence of a number of conditions, health states, health behaviours, and social determinants of health. For example, we will be able to examine the association between recent job loss (by sector) and psychological distress. We will also be able to link the CLSA data collected, for those participants who consented, with existing health registration databases. This will allow us to address questions such as, “How does inpatient length of stay after hip surgery vary by factors such as age, sex, socio-economic status, co-morbid conditions, and region?”

The majority of the core research questions that will be examined over the long-term in the CLSA incorporate a longitudinal component. This can be addressed with a number of statistical techniques. There is interest in the *development* of a process (technically, a stochastic process) as it evolves in time. In this context, time can be understood as calendar time or as age (time of life), as both can be influential in determining outcomes.

For clarity and explanatory purposes, one can consider a stochastic process that describes the movement of individuals through well-defined states (e.g., the states could be defined as disability states, disease states and wellness states) as they age. To create an accurate description of this process, a number of issues will need to be considered simultaneously. For example, calendar time or cohort effect may influence the rate at which participants make a transition from one state to another, as may other covariates such as sex, availability of community support, and so on. Related challenges would be those of (1) assessing the proportion of people with particular covariates who will be in a given state by a certain age, and (2) the distribution of the length of time spent in a given state (i.e., estimation of the sojourn or waiting time distribution).

The area of statistics broadly known as “event history analysis” is used to analyze longitudinal data where transitions are made between two or more states. Survival analysis can be viewed as part of event history analysis. Another statistical approach toward the use of longitudinal data is repeated measures analysis. This broad methodology encompasses techniques for the analysis of characteristics of individuals at several time points (e.g., measurements of clinical variables every three years for 20 years). Both linear and generalized linear mixed models, as well as the use of generalized estimating equations, are suitable methods for repeated measures data.

Clearly, given the magnitude of this study, analyses will involve a wide variety of techniques. Indeed, it is expected that novel statistical methods will be developed as data from the CLSA accumulate.

The CLSA investigators will undertake the core analyses. However, the CLSA is a research platform and thus will provide other scientists with the resources essential to pursuing leading-edge research. Access to the CLSA data and infrastructure will be governed by the Data and Sample Access Committee (DSAC) and a data access policy (Appendix G).

### **5.18. Ancillary Studies and Sub Studies**

The CLSA will be a huge undertaking, with extensive data collection over an extended period. To implement the CLSA in a timely fashion, it has been necessary to limit both the target population under study and the initial study content (core population and core measures). However, it is clear that a number of important scientific questions related to successful aging in specific population subgroups will be posed by researchers in Canada and elsewhere. In addition, many of these questions will only be answerable with particular measurement tools that have not been included in our core measures. For the CLSA to adapt to such developments, we foresee that there will be a demand for the inclusion of ancillary (or add on) studies. For clarity, we define an ancillary study as any investigator driven study requiring new sources of funding that proposes additional data collection involving CLSA participants using any technique, procedure, questionnaire, or observation other than those included in the core data collection for the CLSA (i.e. as set out in the study protocol). While the CLSA recognizes the potential importance of ancillary studies, it is not feasible to consider the inclusion of further ancillary studies until recruitment and baseline data collection are completed.

Since ancillary studies have not been planned in advance, the CLSA's funding envelope does not contain provisions for their conduct. Therefore, any proposed ancillary study will require additional funding prior to implementation. The investigators who propose ancillary studies will be responsible for obtaining the funding for these studies from sources outside of the CLSA.

Investigators who are not part of the CLSA team of investigators will be permitted to conduct ancillary studies using the CLSA research platform. However, these investigators will be required to have a CLSA investigator on their proposal. Data collected as part of the ancillary studies will be stored at the SAC and they will be made available to other investigators after initial analyses have been completed by the research team proposing the ancillary study.

A sub study is defined as an investigator-initiated study that uses existing or available core CLSA data or samples. Investigators with an interest in conducting CLSA sub studies will apply for use of the data through the CLSA Data and Sample Access Committee (see section 8.6).

#### *5.18.1. Examples of Specific Ancillary and Sub Studies*

##### *CLSA Mobility Initiative*

To date, CLSA investigators have successfully applied to CIHR for additional funding to conduct an ancillary study: Canadian Longitudinal Study of Aging-Mobility Initiative (CLSA-MI) Emerging Team (ET). The overall objective of the CLSA-MI is to establish an emerging multidisciplinary team of Canadian researchers who have the common goal of improving the understanding of the dynamics of mobility in aging. This team will use *the framework and platform of the CLSA to address specific research questions related to mobility as a precursor, mediator, and outcome in the health of the population. The following are examples of these research questions:*

- 1) Precursor: How is mobility in mid- and later life associated with physical, psychological, and social functioning?
- 2) Mediator: How does mobility in mid- and later life mediate relationships between determinants of health and health outcomes?
- 3) Outcome: How do physical, psychological, and social functioning in mid- and later life relate to changes in mobility?

These questions will be addressed using measures (e.g., four-metre walk test) that are included in the core set of CLSA measures. However, several new measures will be introduced as part of the CLSA-MI program to elucidate the concept of mobility. These measures will include the Life-Space Assessment (LSA)(129;130), a questionnaire integrating activity and participation at both individual and social levels. Several other questions related to transportation (e.g., driving) will also be added to supplement the core measures. The additional measures will add less than 20 minutes to overall data collection.

#### *CLSA Injury Initiative*

The CLSA investigators received funding from the Public Health Agency of Canada to conduct a study of unintentional fall-related injuries and consumer products. The CLSA data will help fill the following information gaps:

- 1) How can consumer products be used to prevent unintentional injury, in particular falls
- 2) How can consumer product misuse be avoided
- 3) How can consumer product design be improved

Consumer products are considered broadly to include assistive devices. Injury is defined as damage to the body resulting from the transfer of physical energy, whether, mechanical, thermal, electrical, radiant, or chemical, or from the absence of essential energies such as heat.(289) Unintentional injuries are those that do not result from acts of violence (e.g., falls).

Participants identified as having a fall-related injury are asked to complete an additional falls and consumer product module (8-10 minutes). This module contains questions asking for detailed information about the circumstances, nature and consequent healthcare utilization of their fall, as well as whether they were using a consumer product(s) at the time of their fall. These questions will be addressed over a five-year follow-up period. Projections suggest that there will be approximately 7,500 falls available for assessment over this period.

#### *CLSA Veterans Health Initiative*

The CLSA-Veterans' Health Initiative (CLSA-VHI), a project funded in part by Veterans' Affairs Canada. The VHI forms a component of the Population Health Research Strategy of Veterans' Affairs Canada. The goals of the CLSA-VHI are to identify veterans within the CLSA and examine their current health status and their changes in health over time. Another objective is to compare the health of veterans to the health of non-veterans. As part of the CLSA-VHI, a set of 4 Veteran Identifier questions are included in the baseline questionnaires for both the Tracking and the Comprehensive Cohort. We anticipate that approximately 2,000 veterans will be identified within the CLSA.

### *The CLSA-Neurological Conditions Initiative*

Another ancillary study is the CLSA-Neurological Conditions Initiative (CLSA-NCI). This initiative is similar to the mobility and injury initiatives described above. The plan is to establish a research team with a focus on the identification and study of neurological conditions as they present amongst CLSA participants. Prevalence, incidence, risk factors, prognostic factors, and impact on health services utilization could be examined for Parkinson's disease, epilepsy, dementia, and brain injury. The initiative has received funding from the Public Health Agency of Canada – Neurological Health Charities Canada as part of the National Population Health Study of Neurological Conditions.

#### *5.18.2. Process for Applying to Conduct an Ancillary Study*

The conduct of sub studies will require researchers to have access to CLSA data and/or samples. Consequently, the DSAC will evaluate all applications to conduct such studies in a manner consistent with the data access policy outlined in Appendix G. In brief, researchers wishing to conduct an ancillary study will first be required to submit a one-page description of the proposed project (a "letter of intent") to the CLSA. The submission will be reviewed by the SMT or its delegate for its general feasibility, which primarily relates to whether the ancillary data can be collected given the CLSA's existing infrastructure. The review will also assess whether the proposal is in line with the CLSA's informed consent and whether the same or a similar proposal is already under study by other investigators. The Chair will consult with the Directors of the, National Coordinating Centre, the Statistical Analysis Centre, and the Biorepository and Bioanalysis Centre (if applicable) as needed to evaluate the feasibility and appropriateness of the request. If the letter of intent is approved, the applicant will be invited to submit a full proposal (Ancillary Study Request Form) to the DSAC.

If approved, the ancillary study research team will be required to complete and sign an Ancillary Study Agreement and be asked to provide evidence of Research Ethics Board approval from the applicant's Institution. Upon confirmation of completed and signed documentation, the applicant, the National Coordinating Centre and the Statistical Analysis Centre will be notified that the applicant has now been approved to conduct an ancillary study. Any additional data collection involved in the conduct of ancillary studies will be carried out by the CLSA on behalf of the ancillary study research team. The CLSA does not have funding to support the conduct of ancillary studies. Researchers proposing ancillary studies must secure their own funding prior to the commencement of any such study. The ancillary study investigators must discuss budgeting issues with the NCC and SAC as they prepare their full proposal. Funding from approved ancillary study grants will be disbursed to the CLSA in accordance with university and funder regulations.



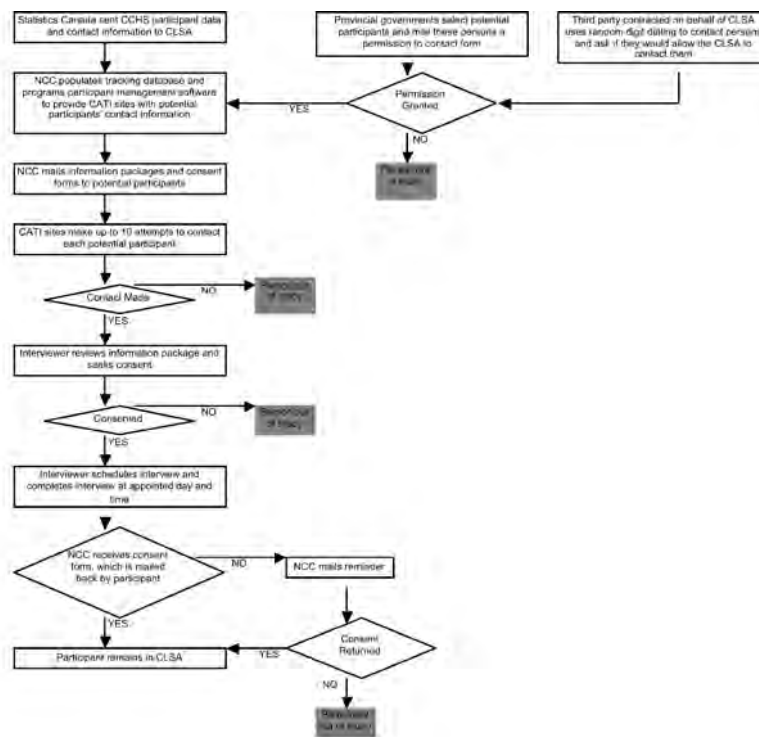
## SECTION 6: DATA COLLECTION AND PROCESSING

### 6.1. Overview

All data for the CLSA Tracking is collected using CATI. For participants recruited from the CCHS Healthy Aging, the initial CATI interview included the Tracking Recruitment Questionnaire for CCHS Healthy Aging Participants. These participants, along with persons recruited from Provincial Health Registration Databases or random digit dialling, will undergo the full 60-minute Tracking Main-wave Questionnaire at each wave of follow-up. Figure 6.1 outlines how participants are recruited into the CLSA Tracking.

At baseline, persons approached for recruitment into the CLSA Comprehensive must agree to an in-home questionnaire interview and a DCS visit. Persons who are unable to complete the interview and visit their local DCS at baseline will be excluded. Each DCS is expected to process 1,000 participants per year. Data collection in the CLSA Comprehensive is conducted using CAPI (in-home interview, DCS visit) and CATI (MC Questionnaire).

Figure 6.1 Participant Recruitment for CLSA Tracking



#### 6.1.1. CAPI and CATI

CAPI and CATI offer important advantages over traditional paper-and-pencil methods of conducting interviews. Interviewer errors are dramatically reduced because the software controls the sequencing of questions and uses previous answers to ‘skip’ around questions that are not applicable for a given

respondent. Incorrect response codes or responses outside plausible ranges are rejected by the software system and the interviewer is prompted for a correction. Contradictory information is also flagged for the interviewer. Since there is no separate data entry step (because interviewers enter responses directly into the computer), data processing errors are minimized, along with the time and expense of later data entry. During questionnaire development and pre-testing, CLSA programmers ensured that the questions were clear and comprehensible to study subjects, thereby reducing errors and increasing the validity of the data that will be collected during the study.

A greater range of questions can be asked using CAPI and CATI as compared to paper-and-pencil-based instruments. The computer system allows the content and sequence of questions to be modified based on a respondent's profile or answers to previous questions. This is a particularly important feature for the CLSA because of the 45- to 85-year age group included in the study population. For example, some questions apply only to women, persons in older age groups, or persons who have retired from work.

CAPI allows for more flexibility in questionnaire design because in-home interviewers may show all materials to respondents on a laptop without the need to carry an assortment of paper-based files.

An important advantage of computer-assisted interviews is that the software upon which interview data are stored can be connected to a central server to enhance data security. The CLSA employs a Virtual Private Network (VPN), equipped with a firewall, to connect all of the study sites to a central server, which is housed at the NCC in accordance with the security provisions outlined in the data access agreements. Data transmission over the VPN is encrypted using industry standard Internet Protocol Security (IPSec). Effectively, no individual-level data are stored permanently at the local DCS or CATI sites. Data are transmitted to the central server at the end of each day.

For laptops assigned to in-home interviewers, the interviewers are required to return to the DCS on a regular basis and download completed interviews off the laptops and onto the central server. Download times are determined according to interviewer schedules. Laptops are equipped with specialized security features that lock or erase content in the event someone attempts to access a laptop without a valid password.

## **6.2. Data Collection – CLSA Tracking**

As previously mentioned, three sampling frames are used to recruit participants into the CLSA Tracking. The first group of Tracking participants (n = 4,462) have already been recruited through Statistics Canada's CCHS Healthy Aging survey; the remaining Tracking participants are being recruited through Provincial Healthcare Registration Databases or random digit dialing.

The participants recruited through Statistics Canada have already completed the CCHS Healthy Aging survey and the CLSA's Tracking Recruitment Questionnaire for CCHS Healthy Aging Participants. The CCHS Healthy Aging survey, which Statistics Canada developed in close collaboration with the CLSA, contains some CLSA core content. However, the CCHS Healthy Aging also contains content that is specific to the needs of Statistics Canada and other stakeholders, but is of lesser relevance to the CLSA. To keep within the timeframe of the CCHS interview, Statistics Canada could not include all of the CLSA core content in the CCHS Healthy Aging survey. Thus, we used the Tracking Recruitment Questionnaire for CCHS Healthy Aging Participants to collect the additional CLSA core content and create a full complement of baseline data on these participants.

Persons recruited into the CLSA Tracking, including participants who already completed the Tracking Recruitment Questionnaire for CCHS Healthy Aging Participants, complete the 60-minute CLSA Tracking Main-wave Questionnaire (Appendix B). Afterward, these participants will complete the CLSA Main-wave Questionnaire once every three years for the duration of the study. A shorter 30-minute MC Questionnaire will be administered mid-wave (i.e., 18 months following each administration of the 60-minute interview). The Tracking Recruitment Questionnaire for CCHS Healthy Aging Participants will not be re-administered at future waves of the CLSA.

Pre-testing of the questionnaires was done to identify problems with the modules and to estimate their time of administration. Table 6.1 presents the core questionnaire content for the CLSA Tracking, along with the point during follow-up when each module will be administered.

**Table 6.1 Timing of Tracking Questionnaire Modules**

Questionnaire Module	Interview		
	Recruitment <sup>1</sup>	CLSA Wave	
		Main Wave <sup>2</sup>	Maintaining Contact <sup>3</sup>
Demographic (e.g., age, sex, education)	X <sup>4</sup>	X	X <sup>4</sup> (age, sex only)
Home Ownership (OWN)		X	
Veteran Identifiers (VET)	X	X	
Height and Weight (HWT)		X	
Smoking (SMK) and Alcohol (ALC)	X <sup>4</sup> (ALC only)	X	
Nutritional Risk (NUR)	X <sup>4</sup>		X
General Health (GEN)	X <sup>4</sup>	X	
Women’s Health (WHO)		X	
Vision (VIS)		X	
Hearing (HRG)		X	
Self-reported Chronic Conditions (CCT)	X <sup>4</sup>	X	
Oral Health (ORH)			X
Pain and Discomfort (HUP)			X
Health Care Utilization (HCU)	X		X
Medication Use (MED)	X <sup>4</sup>		X
Dietary Supplement Use (DSU)	X <sup>4</sup>		X
Functional Status (FUL)		X	
Basic Activities of Daily Living (ADL)		X	
Instrumental Activities of Daily Living (IAL)		X	
Cognition (COG)		X	
Physical Activities (PA2)			X
Depression (DEP)		X	
Satisfaction with Life (SLS)		X	
Posttraumatic Stress Disorder (PSD)	X	X	
Social Networks (SN)		X	
Social Support – Availability (SSA)		X	
Social Participation (SPA)	X <sup>4</sup>	X	
Online Social Networking (INT)			X
Social Inequality(SEQ)			X

Questionnaire Module	Interview		
	Recruitment <sup>1</sup>	CLSA Wave	
		Main Wave <sup>2</sup>	Maintaining Contact <sup>3</sup>
Care Receiving 1/ Formal Care (CR1)	X	X	
Care Receiving 2/ Informal Care (CR2)	X <sup>4</sup>	X	
Care Giving (CAG)		X	
Injury (INJ)		X	
Falls and Consumer Products (FAL)		X	X (number of falls in last 12 months only)
Retirement Status (RET)	X <sup>5</sup>	X	
Pre-Retirement Labour Force Participation (LFP) <sup>5</sup>		X	
Labour Force (LBF) <sup>5</sup>	X <sup>5</sup>	X	
Retirement Planning (RPL)	X <sup>5</sup>	X	
Transportation, Mobility, Migration (TRA)			X
Built Environments (ENV)			X
Income (INC)		X	
Wealth (WEA)			X
Parkinsonism (PKD)			X
Conclusion (CON)			X

<sup>1</sup>The Tracking Recruitment Questionnaire is only administered to those participants recruited through the CCHS Healthy Aging and represents the CLSA core content that was not included in the CCHS Healthy Aging (Appendix B1).

<sup>2</sup>The Tracking Main-Wave Questionnaire is administered to all 20,000 participants at baseline and every 3 years thereafter for 20 years (Appendix B2).

<sup>3</sup>The Tracking Maintaining Contact Questionnaire is administered to all 20,000 participants halfway between each main wave interview and forms the maintaining contact interview (Appendix C6).

<sup>4</sup>Abbreviated version of module administered.

<sup>5</sup>Participants will answer either the Pre-Retirement Labour Force Participation or the Labour Force module depending on their retirement status. The total time for the Main Wave Interview includes three minutes for labour force participation (either pre-retirement or current).

### 6.2.1. Data Management

The NCC assigns a unique study identification number to each participant. Each CATI site is given contact information only for participants in their assigned contact region. CATI sites contact participants in their region, explain the study, obtain informed consent, and conduct the interviews. CATI sites do not retain copies of the contact information or participant data. A complete list of identifying information is stored in a master database at the NCC. Only the lead researchers and authorized research staff have the code to link response records to participants' identifying information.

All study data are kept in a secure location at the NCC. The location is accessible to authorized personnel only. An audit trail of data access is kept at the NCC. All computers with access to study information employ passwords at both the device level and the network level. Participants are asked to send written consent forms by mail directly to the NCC. When not in use, signed consent forms, transportable storage media, and data back-ups are stored in locked cabinets.

### 6.2.2. Questionnaire Administration

In the CATI process, questionnaire items are read by the interviewers and respondents' answers are entered directly into a computer. The interviews are conducted from one of four regionally based CATI

sites (Victoria, Winnipeg, Halifax, and Sherbrooke). Interviews are conducted at thin client workstations linked through a local area network (LAN) using Voice over Internet Protocol (VoIP). All four CATI sites conduct English-language interviews. The Sherbrooke site, based at Université de Sherbrooke, also conducts all French-language interviews across Canada.

Over time, following recruitment into the study, some participants might develop hearing, cognitive, or physical impairments that limit their ability to complete CATI interviews. Steps will be taken to enhance the likelihood of these participants being able to complete follow-up interviews. These steps could include assistance in questionnaire completion or having a questionnaire administered in a different mode. Information concerning the ability of a participant to complete one of the components of the study is recorded so that subsequent data collection phases can use the most effective method of data collection for that participant.

### *6.2.3. Data Quality Control*

Each CATI site is responsible for checking completeness and accuracy of data during the interview. With participant permission, modules of the interview are recorded for quality control. CATI managers also listen in on 10% of all live interviews. The CATI software is programmed to flag missing or inconsistent information such that data queries can be made in real-time. Figure 6.2 is a data collection flow diagram for the CLSA Tracking. The NCC forwards the de-identified data to the Statistical Analysis Centre (SAC). The SAC checks the data for missingness, outliers, improper skip patterns, implausible values, and other anomalies.

The SAC links subsequent waves of data based on the unique identifiers and does not have access to identifying information such as name or contact information. Having all data centrally located at the NCC during data collection ensures maximal data security, efficient management, and quality control.

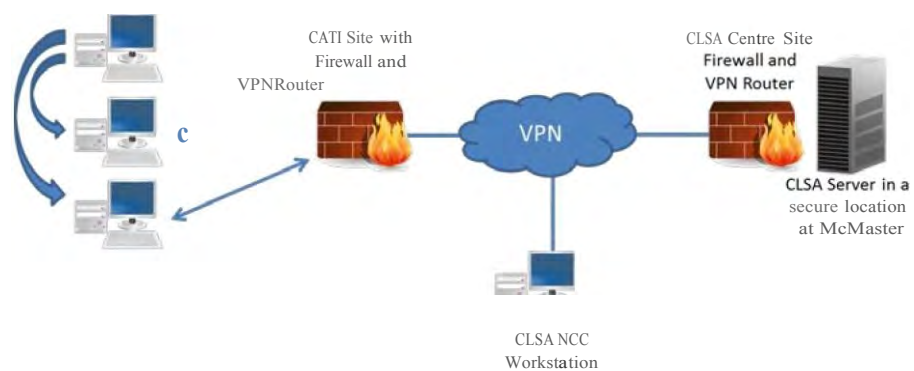
## **6.3. Data Collection – CLSA Comprehensive**

### *6.3.1. Baseline In-home Interview*

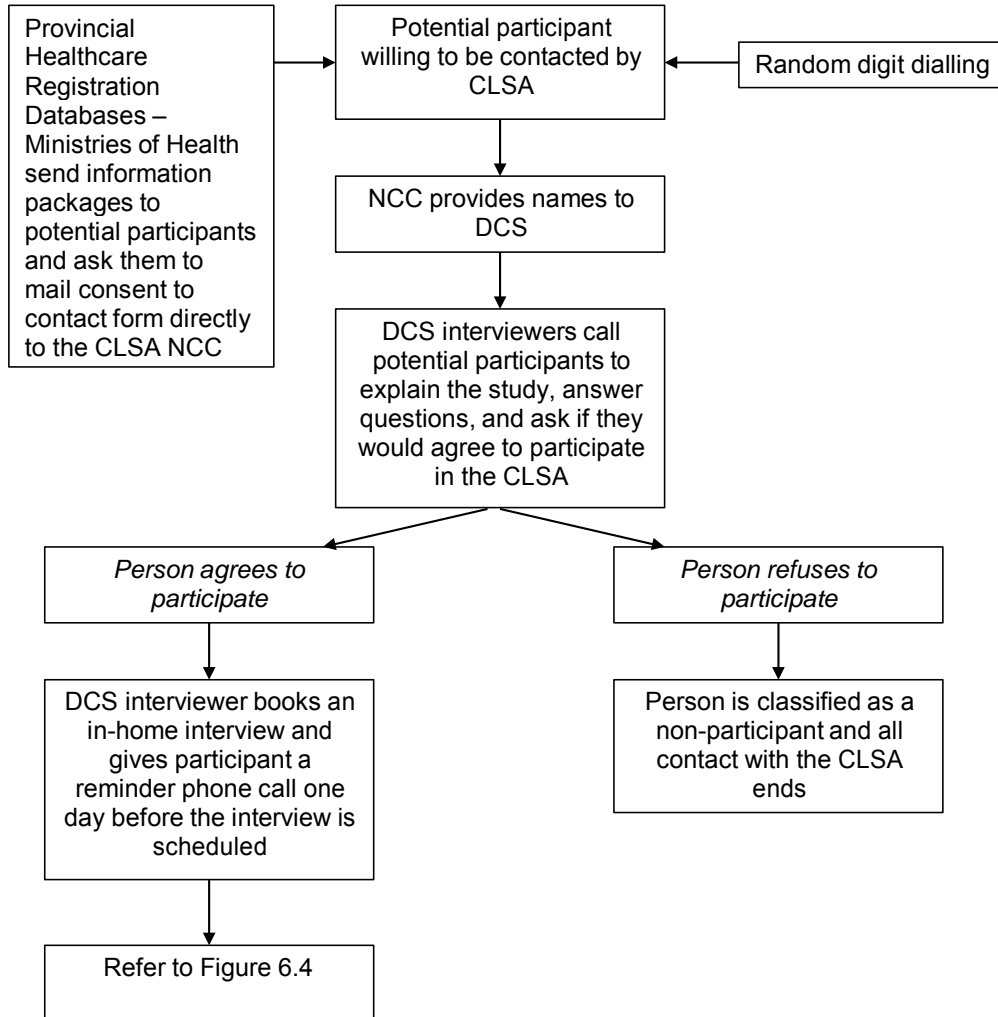
The baseline, in-home, CLSA interview consists of two parts, informed consent, and administration of the Comprehensive Main-wave In-home Questionnaire. All interviewers are equipped with a photo identification card bearing the CLSA logo, interviewer's photograph, and the interviewer's name. Interviewers are required to show this card to participants before entering their homes. Interviewers telephone participants prior to scheduled interviews to confirm the day and time, as well as to ask participants to lay out their medications. Figures 6.3 and 6.4 depict the recruitment and data collection flow for the CLSA Comprehensive.

**Figure 6.2 CLSA Tracking Data Collection Flow Diagram****Data Sharing Protocol**

1. CATI software on CLSA server at McMaster University
2. CATI and NCC workstations set up with encryption (passwords)
3. Contact information and data are NOT stored or saved at individual CATI sites' or NCC computers
4. Data will always be stored at CLSA secure server



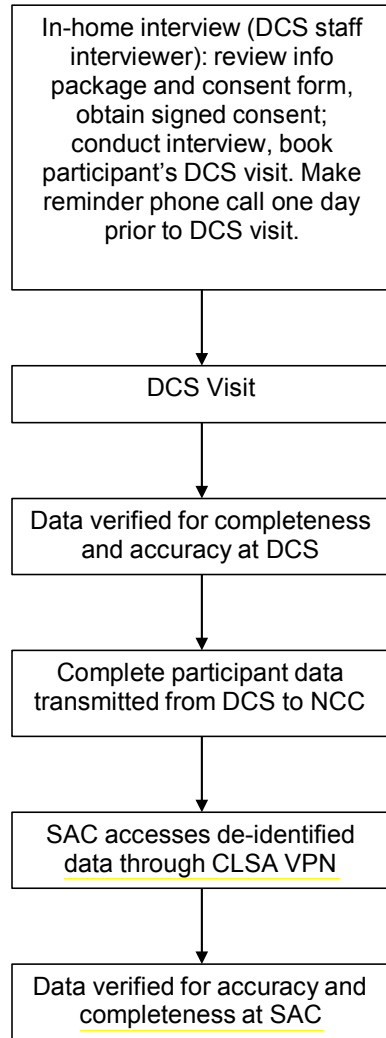
**Figure 6.3 CLSA Comprehensive: Process for Contacting Potential CLSA Participants**



6.3.1.2. *Comprehensive Main-wave In-home Questionnaire Content and Administration*

The Comprehensive Main-wave In-home Questionnaire contains the content described in Table 6.2 and takes approximately 60 to 75 minutes to administer on average. An additional 10 to 15 minutes is required for the informed consent process.

**Figure 6.4 CLSA Comprehensive: Baseline Data Collection**



Note: Data transmission will be conducted via the CLSA's Virtual Private Network (VPN).



**6.3.1.1. Informed Consent**

During the in-home interview, interviewers obtain participants’ informed consent electronically using a signature pad (see Appendix D for the consent form). Participants are also asked whether they will consent to provide biospecimens (i.e., blood and urine) and their health insurance numbers (HIN). Refusal on the part of participants to provide biospecimens or HINs does not exclude them from the study. All participants are also asked for the name of an alternate contact person who knows them well and would be aware of their whereabouts should relocated between data collection waves. In addition, participants aged 70 years or over are asked to provide the name and contact information for an alternate informant who ideally could act as a proxy if they are not able to participate in a CLSA follow-up interview (see section 5.9). In-home interviewers obtain the proxy information from participants, who are asked at the DCS visit to sign consent to contact proxy form.

Participants are advised that they may withdraw from the study at any time and they are provided with information on how to do this. The interviewer explains the DCS visit. The study explanation and informed consent process take approximately 15 to 20 minutes. Participants are asked to consent to participate in the longitudinal component of the CLSA. Since the CLSA entails multiple waves of data collection from each participant, their continued consent and proxy information will be reconfirmed at each study contact; participants will be reminded of their option as it relates to continuing to participate in the study.

**Table 6.2 Timing of Comprehensive Questionnaire Modules**

Questionnaire Module	Interview		
	Main Wave <sup>1</sup>		Maintaining Contact <sup>2</sup>
	In-home	DCS	
Demographic (includes age, sex, education, home ownership)	X		X (age, sex only)
Veteran Identifiers (VET)	X		
Smoking (SMK) and Alcohol (ALC)	X		
Nutrition (NUT)	X		
Nutritional Risk (NUR)			X
General Health (GEN)	X		
Women’s Health (WHO)	X		
Vision (VIS)	X		
Hearing (HRG)	X		
Oral Health (ORH)			X
Injuries (INJ) & Falls and Consumer Products (FAL)	X		X (number of falls in last 12 months only)
Snoring (SNO)			X
Pain and Discomfort (HUP)			X
Health Care Utilization (HCU)			X
Dietary Supplement Use (DSU)			X
Basic Activities of Daily Living (ADL)	X		
Instrumental Activities of Daily Living (IAL)	X		
Life Space Index (LSI)	X		
Physical Activities (PA2)			X
Personality Traits (PER)			X

Questionnaire Module	Interview		
	Main Wave <sup>1</sup>		Maintaining Contact <sup>2</sup>
	In-home	DCS	
Psychological Distress (K10)			X
Satisfaction with Life (SLS)	X		
Posttraumatic Stress Disorder (PSD)	X		
Social Networks (SN)		X	
Social Support – Availability (SSA)		X	
Social Participation (SPA)		X	
Social Inequality(SEQ)			X
Online Social Networking (INT)			X
Care Receiving 1/ Formal Care (CR1)	X		
Care Receiving 2/ Informal Care (CR2)	X		
Care Giving (CAG)	X		
Retirement Status (RET)	X		
Pre-Retirement Labour Force Participation (LFP)	X		
Labour Force (LBF)	X		
Retirement Planning (RPL)	X		
Transportation, Mobility, Migration (TRA)			X
Built Environments (ENV)			X
Income (INC)	X		
Wealth (WEA)			X
Chronic Conditions – Symptoms		X	
Neuropsychological Battery <sup>3</sup>	X	X	
Medications and Dietary Supplement Use	X <sup>4</sup>		
Sleep	X		
Conclusion (CON)			X

<sup>1</sup>The Comprehensive Main-Wave Questionnaire is administered to all 30,000 participants at baseline and every 3 years thereafter for 20 years. Part of the content will be collected at the In-Home interview (Appendix C1) and part will be collected at the Data Collection Site (Appendix C2-5).

<sup>2</sup>The Comprehensive Maintaining Contact Questionnaire is administered to all 30,000 participants halfway between each main wave interview (Appendix C6).

<sup>3</sup>Rey Auditory Verbal Learning Test, Animal Naming Test, and Mental Alternation Test are administered during the in-home interview; the remaining components of the neuropsychological battery are administered at the DCS.

<sup>4</sup>DIN Information will be recorded directly from prescription medications in the CLSA Comprehensive.

### 6.3.2. Data Collection Site Assessment

Participants recruited into the CLSA Comprehensive undergo an in-depth assessment at a DCS within 25 kilometres of their home (50 kilometres in DCS territories with less urbanized environments such as St. John's, Halifax, and Sherbrooke). At the DCS, participants undergo a physical assessment. As well, they complete the Comprehensive Main-wave Disease Symptoms Questionnaire and neuropsychological battery to elicit information about chronic conditions and neuropsychology. Three components of the neuropsychological battery (i.e., Rey Auditory Verbal Learning Test, Animal Naming Test, and Mental Alternation Test) are administered during the in-home interview. Participants who consented to biospecimens donation provide a blood sample and a urine specimen. All of the evaluations and tests are administered according to standardized protocols. To defray the costs of attending a DCS visit (i.e.,

transportation, parking), participants are reimbursed \$30. The payment is made upon completion of the visit.

All CLSA personnel undergo detailed training in all aspects of data collection. The training is standardized across all DCS.

6.3.3. Recording of Participant Data

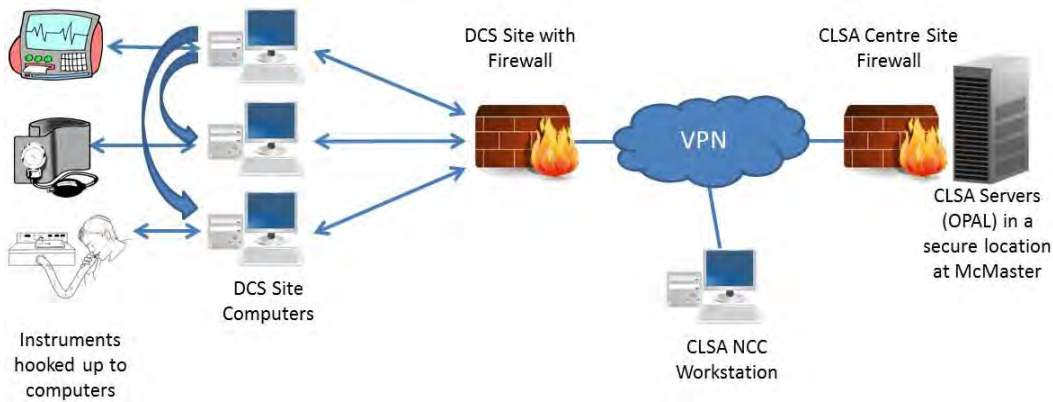
Besides questionnaire-based data, data pertaining to the following items are recorded during the CLSA Comprehensive: participant baseline information, physical assessment measures, and biospecimens. Furthermore, ‘process’ data are recorded about unanticipated events at the DCS, protocol deviations, and miscellaneous comments (e.g., problems with DCS equipment). To accomplish these data recording tasks, we have drafted case report forms (CRFs). These CRFs were input into CAPI software so that all data collected during a DCS visit are immediately recorded electronically in a ‘paperless’ environment.

We selected devices and machines for use at the DCS that permit immediate download of actual instrument readings directly into our data collection software. These downloads are transmitted to the NCC at the end of each workday. Figure 6.5 is a data collection flow diagram for the CLSA Comprehensive Cohort.

Figure 6.5 CLSA Comprehensive Data Collection Flow Diagram

Data Sharing Protocol

1. Onyx software on DCS server at each site, exports data to OPAL Server at McMaster
2. DCS and NCC workstations set up with encryption (passwords)
3. Contact information and data are NOT stored or saved at individual DCS sites’ or NCC computers
4. Data will always be stored at CLSA secure server at McMaster



#### 6.3.4. Data Collection Site: Participant Flow-through Example

DCS interviewers telephone participants whom they previously interviewed in the home to remind them about their upcoming DCS visit and to confirm their attendance. This reminder telephone call is made one day prior to the scheduled visit.

Room 1: Upon arrival at the DCS, participants proceed to the reception desk, where a research assistant verifies their name and appointment time, and logs them into the system along with the following information:

- i. Last name, middle name, and first name;
- ii. Date of birth;
- iii. Address;
- iv. Contact person and contact information; and
- v. Consent to contact proxy for participants aged 70 years or over.

The research assistant also assigns participants a visit identification number specific to the current visit. This number is different from, but linked to, participants' unique CLSA identification numbers.

Participants' check-in times are electronically recorded as they are logged into the system.

Room 2: A research assistant administers a brief questionnaire to assess potential contraindications to the tests that are performed during the DCS visit (Appendix C2). If a contraindication is found, the information is immediately entered into the database. When a participant with a contraindication arrives at the data collection room where the contraindicated procedure would be administered, the person staffing the room is alerted to forgo the procedure.

Room 3 – Participant's waist-hip ratio, weight, and standing and sitting height are measured here. Other measures in this room include heart rate, blood pressure, ECG, carotid ultrasound, and spirometry.

Room 4 – The DXA machine is located in a room designed to manage x-ray emissions. Participants are scanned for bone density, lean muscle mass, and aortic calcification.

Room 5 – This is an interview room where participants complete some components of the neuropsychological battery (i.e., event-based Prospective Memory Test, Stroop, Controlled Oral Word Association Test, and Choice Reaction Time), a hearing test, and a questionnaire on social networks, availability of social support, and social participation.

Room 6 – Located in the DCS corridor, participants do the 4-metre walk test and the timed get-up-and-go test.

Room 7 – Physical measures continue in this room with standing balance, chair rise, and grip strength. A vision test (preceding grip strength) is also conducted here. The vision test includes a visual acuity chart, tonometer, and retinal camera.

Room 8 – Another interview room where participants undergo the time-based Prospective Memory Test and answer the disease symptom questionnaire.

Room 9/10 – Once all measures are complete, participants who agree to provide blood and urine samples proceed to the phlebotomy room. Snacks are available after this room.

Room 11 - Participants return to reception for ‘check-out’ and receive \$30 to defray the cost of attending the DCS visit. Participants also get a computer printout of some of their DCS measurement results. The printout includes body mass, waist-hip ratio, blood pressure, hearing, visual acuity, lung capacity, bone mineral density, and percent body fat.

Appendix H1 contains a more in-depth description of participants’ flow through the DCS.

The order of participant flow through the DCS was initially patterned after the procedures adopted by the United Kingdom (UK) Biobank.(290) We tested and refined the initial order in pilot studies conducted at the Hamilton and Montréal DCS locations.

#### *6.3.5. Home Data Collection Protocol*

At future waves of data collection following the baseline assessment, some participants may become unable to travel to their local DCS and the CLSA will adapt to accommodate them. If a participant is capable of traveling, but has no means of transportation, then efforts will be made to arrange return transportation so the participant may travel to the DCS. When provision of transportation is unfeasible (e.g., participant lives in a semi-rural area and travel by taxi would be prohibitively expensive) or impractical (e.g., participant has a health condition precluding travel), the CLSA will assess whether the layout of the participant's home would permit the collection of data that would normally be collected at the DCS. If so, the CLSA will ask the participant for permission to schedule an in-home assessment to replace the DCS visit. Trained staff from the DCS will conduct the in-home assessments.

All DCS-based questionnaires will be adapted to the in-home environment using CAPI software installed on laptops. For the physical performance measures, the in-home assessment will include grip strength, timed get-up-and-go, chair rise, height, weight, blood pressure, body fat percentage, and heel bone density. We will also conduct spirometry. With the exception of measurements of bone density and body fat percentage, these assessments will be done using the same equipment as used at the DCS.

#### *6.3.6. Validation of Home Data Collection Equipment for Bone Density and Lean Muscle Mass*

A portable ultrasound device will be used to measure bone density during in-home assessments. The Hologic Sahara BMD Ultrasound Bone Density Densitometer is a Quantitative Ultrasound (QUS) device that is fastened to the ankle and heel to obtain an extrapolated measure of bone density. The device has been shown to be a simple and non-invasive tool in research settings for diagnosing osteoporosis. A recent study comparing QUS measurements to DXA concluded that in the case of low availability of DXA equipment, QUS devices appear to be the most suitable alternative for osteoporosis diagnosis.(291)

Body fat during in-home assessments will be measured using the Tanita BF-350 Body Composition Analyzer. This device measures the impedance or opposition to the flow of an electric current through body fluids contained mainly in lean and fat tissue. A study of the validity of measurements with a Tanita analyzer, compared to underwater weighing among male subjects, found no systematic differences between the two methods (mean difference,  $0.07 \pm 3.5\text{kg}$ ). (292) Another study found similar results among a group of obese women when comparing underwater measurements with measurements taken using the analyzer ( $r=0.78$ ). (293)

### *6.3.7. Throughput Targets for Data Collection Sites*

Interviewers contact participants on weekday afternoons and early evenings to book in-home interviews and DCS visits. Each DCS endeavours to perform five clinical assessments per day. A 10-month operating schedule is followed to provide for two months (eight weeks) of down time per year to account for a Christmas shutdown (two weeks), summer holiday shutdown (two weeks), statutory holidays (e.g., Canada Day) and unforeseen events (e.g., snow days), as well as to build-in 'recovery time' (i.e., days reserved for re-scheduling missed in-person or in-home visits). Through pilot work conducted at the Hamilton and Montréal DCS locations, we determined that five assessments per day would be a reasonable target to achieve.

Based on this 10-month schedule and assuming five DCS visits per day, each DCS is targeted to complete 25 visits per week, 100 visits per month, and 1,000 visits per year. The local site principal investigator monitors throughput on a weekly basis and ensure the weekly and monthly targets are met.

We have not reached the target of five daily visits at all DCS locations during the first year of Comprehensive recruitment. This is due to the need to train new staff, as well as the learning curve involved in conducting all of the tests. DCS locations are moving closer to the daily visit target and we expect all locations to meet the target during the second year of recruitment.

### *6.3.8. Safety Issues for In-home Interviewers and DCS Staff*

The CLSA has developed practical procedures to ensure participant and staff safety in all components of the study. The procedures are incorporated into the appropriate training manuals and study documentation. Summary charts are posted at each DCS for quick and acceptable responses in case of unexpected events. Throughout the study, all CLSA staff are given proper training to ensure their safety and the safety of participants.

#### *6.3.8.1. Data Collection Site – Staff Immunization*

Guidelines are available to assist CLSA staff in determining their immunization needs. Many CLSA sites are located within institutions that have pre-existing immunization guidelines. In such cases, the sites in question abide by these pre-existing guidelines.

#### *6.3.8.2. Data Collection Site – Cleanliness*

Workstations at the DCS are kept clean and wiped with appropriate sterilizing agents after each use. If any blood is spattered on a workstation, the stain is wiped immediately. Site staff wear protective gloves during phlebotomy and handling of biospecimens.

Needle disposal boxes are available for all personnel drawing blood samples. Needles are released from adapters directly to the needle disposal box; reheating will be avoided. The disposal boxes are replaced every second day to prevent overflow. Hand sanitizers are placed at the entrance/exit, in washrooms, and in the corridors.

#### *6.3.8.3. Home Visits – CLSA Interviewer Identification and Authenticity*

All CLSA interviewers have custom identification cards showing their names and photographs. Interviewers show the cards to participants at the doorstep, prior to gaining entry to the home. Interviewers also have a phone number that the participant can call to verify the interviewer's authenticity.

#### 6.3.8.4. Home Visits – Safety Guidelines for Interviewers

All interviewers are trained to follow a code of conduct for their safety in the field. In addition, a specific period is defined in which interviewers are permitted to schedule interviews. Interviewers are required to telephone the reception desk of their local DCS to confirm the end of an interview.

#### 6.3.8.5. Emergency Protocols

Standard guidelines in case of emergencies (e.g., needle stick injuries or participants who faint) are available at each site and provided to each staff member. CLSA staff are made aware of, and trained for, emergency situations. Emergency contact numbers (or telephone extensions for DCS located in hospitals) are provided to each DCS and interviewer. CLSA staff are required to report all events to their site principal investigator and complete an incident report. Debriefing sessions are held between the investigator and employee to discuss the situation and ensure that standard guidelines were followed. In exceptional or unforeseen situations, supervisors can contact the NCC for guidance. All emergencies are logged and the NCC is informed regularly of these events. The CLSA Operations Committee decides whether the occurrence of an emergency requires revisions to the guidelines for handling emergencies.

During the course of a home interview or DCS visit, a CLSA employee may suspect that a participant is being subjected to physical or emotional abuse or neglect. The employee will report all such suspicions to the local DCS site investigator, who will notify the relevant authorities for follow-up in accordance with provincial law.

## SECTION 7: BIOSPECIMENS

### 7.1. Overview

Collection of biospecimens is being carried out at each Data Collection Site (DCS). The biospecimens are shipped to the Biorepository and Bioanalysis Centre (BBC) at McMaster University for long-term storage. The guiding principles for development of the biospecimens protocol are to have an efficient and standardized sample collection procedure for high quality and well-annotated samples, to minimize sample degradation, to maximize effectively the variety of specimen types from blood, the number of aliquots, and the volume. This will provide a wide range of sample types to use for answering diverse scientific questions and measurement of new biomarkers throughout the life of the CLSA and beyond.

Analysis of the biospecimens will occur at each DCS for basic hematological tests only (see Section 7.11.1). Other biochemical tests will be conducted at the BBC at McMaster University, the Genetic and Epigenetic Centre (GEC) in Vancouver, and other research laboratories when appropriate.

The biospecimens collection manual along with standard operating procedures provides comprehensive details for consistent collection, processing, transport, storage, and tracking of specimens.

### 7.2. Quality and Standards

Since many analyses of the biological material collected by the CLSA will be carried out after recruitment and baseline assessment, “best practice” methods, defined as “strategies, systems, processes, and methodologies that should be used in biospecimens and data collection, storage and distribution, to provide a robust resource for biospecimens-based research”, (294) will be utilized to ensure the long-term stability of a wide range of analytes. The best practice documents of the International Society for Biological and Environmental Repositories(295) and the National Cancer Institute(296) provide guidance for preservation of biospecimens integrity. The acquisition, handling, shipment, storage, and analysis of biospecimens constitute one of the largest and most expensive aspects of the CLSA, emphasizing the importance of standardized protocols to minimize process variation and yield unbiased samples for the study. Each step of the process will be tracked and these data entered into LabWare, our Laboratory Information Management System (LIMS).

Given the importance of this aspect of the CLSA, feasibility work was conducted to explore whether existing clinical laboratories in both private and public settings have the capacity to execute these protocols for the collection, processing, freezing, temporary on-site storage and shipment of biospecimens, including all documentation needed to complete the laboratory visits. The efficacy of these procedures to minimize error and provide consistently high biospecimens quality was determined empirically.(297) We found that the CLSA biospecimens collection and handling protocol consistently allowed technologists to process the biospecimens at the collection site in compliance with the recommended time from collection to freezing of aliquots of up to two hours.(297)

By completing the processing steps required to maximize biospecimens integrity at each local DCS, the CLSA will control pre-analytical variables that could preclude specimens from analyses for specific analytes, or result in confounding of analytical results by biospecimens degradation due to delayed processing. To provide a consistently high level of quality control for all CLSA biospecimens, a maximum of six participants will provide biospecimens per day at each data collection site. All biospecimens processing is done at the data collection site, and biospecimens are frozen and shipped in nitrogen vapour shippers that maintain the specimens in the frozen state for at least seven days (allowing



for unforeseen delays in transit without compromising specimen integrity). Each nitrogen vapour shipper will be equipped with a data logger to track temperature changes during transit.

### **7.3. Biospecimens Types, Tube Types, and Aliquots**

Only blood and urine specimens will be collected from participants in the CLSA Comprehensive. These are the most common biospecimens types used for research and diagnostic purposes. They were selected based on feasibility and cost of acquisition, processing and storage, as well as predictive value for subsequent health outcomes. Blood samples are non-fasting and the urine sample is random. The benefit of non-fasting blood and random urine samples is that it allows each DCS to schedule participants throughout the day. However, we will also collect parameters pertinent to interpretation of biomarker tests such as when the last meal was eaten, alcohol consumption, and medications as some biomarkers may be affected by these factors.

A list of potential analytes were compiled by the CLSA Biological Working Group members and used as a guide to determine the type of blood collection tubes and their proportion for the overall collection to allow as broad a range of future potential uses. Descriptions of the biospecimens to be collected are described in Table 7.1. The total number of individual aliquots to be stored for each participant was based on the need to provide sufficient quantity for rapid and multiple research questions to be answered while keeping storage costs reasonable. Aliquot volumes of 0.5-mL were chosen to facilitate sample use so refreezing of the sample would not be done. Thawing and refreezing samples decreases the integrity of a sample and can produce inaccurate measurements. Consideration was also given to sample usage (about 20% per year) and participant attrition rate.

Genetic and epigenetic analyses are an important component for the CLSA and it is expected many researchers will request DNA. To provide ample quantity for different applications four types of specimens will be collected.

Whole blood from ACD tubes are collected and diluted 1:1 with dimethyl sulfoxide (DMSO) to preserve cells. Cryogenic maintenance of living blood cells allows for the optional production of immortalized cell lines for generation of high molecular weight DNA, as well as telomere studies and functional assays.

Whole blood from EDTA tubes is stored on Whatman FTA paper in microwell plates (GenPlates, IntegenX, and Pleasanton, CA) at room temperature. Dry storage of whole blood in microwells is a convenient way to store many aliquots with each containing a small amount of DNA. These samples can be successfully used for SNP analysis strategies including genome wide association studies and PCR applications.

Larger volumes of DNA and RNA are available from samples of buffy coat obtained from EDTA blood. Blood collected in CPT tubes (BD, Mississauga, ON) will allow for efficient isolation of mononuclear cells that are done in each DCS.

**Table 7.1 Biospecimens collection parameters.**

Type	Volume (mL)	Number	Total volume (mL)	Number of aliquots
<b>1. Citrate</b>				
<i>3.2% buffered sodium citrate solution, 0.109 M</i>				
Plasma	2.7	1	2.7	2
Plasma, platelet poor	2.7	1	2.7	2
<b>2. Serum</b>				
<i>Spray coated silicone and micronized silica particles</i>				
Serum	10	1	10	8
<b>3. Heparin</b>				
<i>Lithium heparin, 90 USP</i>				
Plasma	6	1	6	6
<b>4. EDTA</b>				
<i>Spray coated K<sub>2</sub> EDTA, 10.8 mg</i>				
Plasma	3	1	3	0 <sup>1</sup>
Plasma	6	3	18	6
Buffy coat			(2)	4
Whole blood			(1)	2
Whole blood			(1)	(96) <sup>2</sup>
<b>5. ACD</b>				
<i>Trisodium citrate, 13.2g/L; citric acid, 4.8 g/L; and dextrose 14.7 g/L, 0.4 mL</i>				
Whole blood	3	1	3	2
<b>6. CPT</b>				
<i>Sodium citrate 0.45 mL 0.1 M and Ficol<sup>TM</sup> medium</i>				
Mononuclear cells	8	1	8	6
<b>Urine collection container</b>				
Urine	60	1	2	4

Tubes are listed according to the order they will be drawn

<sup>1</sup> Baseline hematology tests performed at the DCS. No aliquots are stored.

<sup>2</sup> Collected only at first collection. Aliquots (10  $\mu$ L) are stored in GenPlate microwells.

#### 7.4. Collection Procedure

BD Vacutainer tubes (BD Diagnostics, Franklin Lakes, NJ) will be used to collect approximately 50 mL of blood by standard venipuncture. A urine collection container is provided for each participant to obtain a random urine sample. Detailed instructions for collecting a quality sample including phlebotomy technique draw order, volume of blood, and number of inversions to mix the additives are provided in the specimen collection manual. These instructions are based on the CLSI guideline H03-06 Procedures for the Collection of Diagnostic Blood Specimens by Venipuncture.

#### 7.5. Storage System

##### 7.5.1. Tubes

Sample archiving will be achieved utilizing 500- $\mu$ L V bottom, screw-top tubes (Matrix Tubes, Thermo Fisher Scientific, Carlsbad, CA). Each tube has a unique laser-etched 2D barcode located on the bottom and can be stored down to  $-185^{\circ}\text{C}$ . These tubes are stored in open bottomed boxes specifically designed for fast scanning and retrieval of chosen samples. The standard 96 well format will also allow the potential for future ‘pick and place’ robotic retrieval and storage box compression (‘defragging’).

### 7.5.2. *Microwell Plates*

The CLSA will utilize GenPlates (IntegenX, Pleasanton, CA) for dry storage of DNA. Each plate will hold 96 10- $\mu$ L aliquots of blood for 3 participants in 3 discrete zones. After the EDTA whole blood is applied to the FTA wells, they will be dried for a minimum of 16 hours in the FastDryer and then sealed with an adhesive seal.

### 7.5.3. *Nitrogen freezers*

Over the 20 years of the CLSA biospecimens collection, approximately 5 million aliquots will be stored in 31 nitrogen freezers. Since these biospecimens will be stored for an extended period, nitrogen vapour storage will be used to avoid the potentially deleterious effects of higher storage temperatures. The nitrogen freezers are auto filled from a bulk nitrogen supply tank outside the storage facility and piped in through vacuum-jacketed pipelines.

### 7.5.4. *Personal Archive*

Blood collected in GenPlates are placed into the Personal Archive, a room-temperature archiving system from IntegenX. Dry storage represents a significant cost reduction compared with liquid storage as no nitrogen freezers or refrigerators are needed. The retrieval process can be automated using standard robotic systems since the dimensions of GenPlates meet the SBS standards.

## 7.6. **Biospecimens Processing**

Biospecimens are processed in each DCS by a trained research technician or laboratory technologist according to instructions provided in the collection manual and standard operating procedures. An overview of this process can be found in Appendix I. A material transfer agreement will be put in place between all DCS institutions and McMaster University.

### 7.6.1. *Centrifugation*

All blood collection tubes requires centrifugation except the ACD tube (see 7.6.2), and one EDTA tube which is used for hematology testing at the DCS. A swinging bucket rotor centrifuge is used for all centrifugations (2000 g, 10 min). A second centrifugation (1500 g, 5 min) will provide the platelet poor plasma fraction.

### 7.6.2. *ACD tube*

Two 0.25 mL volumes of ACD blood will be mixed with 0.25 mL DMSO (20% in RPMI growth medium) to obtain two 0.5 mL aliquots. Controlled freezing of ACD/DMSO tubes for cell cryopreservation is done using the low cost alcohol free CoolCellfreezing container (BioCision, Mill Valley, CA) instead of an expensive rate controlled freezer.

### 7.6.3. *CPT tube*

Following the first centrifugation (1500 g, 20 min) most of the plasma is aspirated off and discarded. The remaining plasma and cell layer (composed of mononuclear cells and platelets) is transferred to a 15-mL conical centrifuge tube and resuspended in phosphate buffered saline (PBS, without  $\text{Ca}^{2+}$  or  $\text{Mg}^{2+}$ ) followed by a second centrifugation (1500 g, 10 min). The supernatant is removed and the washing process is repeated once, followed by resuspension in PBS.

### 7.6.4. *Aliquoting into Matrix tubes*

An adjustable pipette set at 500  $\mu$ L is used to transfer prepared blood fractions and urine into Matrix tubes. A template box with defined areas for each fraction type is used to ensure the products of each

source container are transferred into the appropriate tubes. The layout of the storage box is programmed into the biospecimens accessioning database of LabWare so each type of aliquot is automatically assigned to the specific barcodes in each collection at the time of scanning. Efficient scanning is achieved since the 2D barcodes are exposed at the bottom of the box and can be scanned together, rather than individually. The time from collection of the biospecimens to the freezing of the processed aliquots will be within two hours, with the exception of the CPT tube, which will be within 6 hours, for all visits. All tubes are transferred from the template box to a permanent storage box, frozen and stored temporarily at the DCS at  $-80^{\circ}\text{C}$  until shipment in vapour shippers to the BBC. Each permanent storage box is labelled with a unique barcode number. The individual aliquots are logged into the specific box using this barcode at the time the aliquots are transferred to the box.

#### *7.6.5. Aliquoting into GenPlates*

Whole blood (1-mL) from an EDTA tube will be transferred into a reagent reservoir and pipetted into the GenPlate wells using a 12-channel pipette. By using a multi-channel pipettor, only 6 aspirations are required to dispense 96  $10\ \mu\text{L}$  volumes.

### **7.7. Shipping and Receiving**

#### *7.7.1. Shipment of Cryovials*

Vapour shippers are used to transport frozen samples to the BBC. Each vapour shipper is charged with liquid nitrogen at the BBC and shipped by overnight courier to each DCS. This process ensures control or proper filling and eliminates the need for each DCS to have a supply of nitrogen to fill the shippers. All vapour shippers are equipped with data loggers to record temperatures during transit and be identified by a unique barcode number linked to its serial number. Once charged, the shipper will retain its temperature ( $-160^{\circ}\text{C}$ ) for at least seven days. Shipping of the pre-charged vapour shippers will occur on a weekly basis. Upon arrival at the DCS, the vapour shippers are filled with up to 12 Matrix boxes representing one week of biospecimens collection. As each Matrix box is transferred into the vapour shipper, the barcode on the box is scanned. Using LabWare, an electronic manifest is created listing the number of Matrix boxes and all tubes contained within them. FedEx is used to ship each vapour shipper by overnight courier to the BBC once a week. Once the FedEx Airway Bill number for each vapour shipper is obtained, it is entered into the specific manifest matching that vapour shipper and e-mailed to the BBC.

#### *7.7.2. Shipment of GenPlates*

GenPlates, are packaged with a desiccant pack in a zipper locked envelope and sent overnight to the BBC by courier. The barcode on each plate is scanned as they are transferred into the shipping envelope. The LIMS produces a paper manifest to be included in the shipping envelope and it is e-mailed to the BBC. This is a weekly shipment following the same shipping schedule as for the vapour shippers.

#### *7.7.3. Receipt of Biospecimens*

On receipt of the shipment manifest, the BBC is alerted that a shipment is being initiated by a specific DCS for delivery the following day. On receipt, each Matrix box barcode is scanned into the biorepository accessioning database of LabWare confirming receipt. Further verification occurs by scanning the full box using the VisionMate high speed, single rack 2D barcode reader. The LIMS runs a comparison between the tube barcodes by position on the electronic manifest to those the barcodes scanned. Any discrepancies are flagged and require manual confirmation on a tube-by-tube basis. The data log for each vapour shipper is downloaded and linked to the tubes in each storage box transported in that vapour shipper. Similarly, the barcode on the GenPlates is scanned and compared to the paper manifest to confirm accuracy. Any discrepancies are investigated and documented with the plate.

## **7.8. Identification and Tracking**

### *7.8.1. Supplies*

All supplies will be received at the BBC and packaged for monthly shipment to each DCS. This will ensure all supplies used by each DCS are the same (standardized) and that all time sensitive supplies are tracked and utilized before their expiry date. Barcode labels for the supplies will be generated centrally in order to prevent duplication of sequences. Lot numbers and expiry dates will be tracked centrally by the barcode numbers.

### *7.8.2. Biospecimens*

Each blood collection tube type, urine collection container, and aliquot tube is scanned at each stage of processing and handling. The frequency of scanning ensures all steps in the process are monitored to reduce error. This time stamping also provides a detailed history of the biospecimens from collection to storage while in the DCS.

## **7.9. Security and Safety**

The nitrogen freezers at the biorepository are equipped with CryoMORE (Air Liquide Healthcare, Houston TX), a continuous internal monitoring system with a dedicated server to capture biospecimens storage conditions in each individual cryofreezer. The system automatically communicates critical conditions such as changes in the supply of nitrogen or critical temperature levels to at least two local key personnel, as well as two additional distant operators (one in Ontario and one in Italy) who have the ability to remotely initiate, filling of individual nitrogen freezers if necessary. The storage vessels and environmental control system have been installed with a high degree of redundancy, in the event a freezer or freezer monitor should fail. The installation of a bulk tank minimizes dependency on timely delivery of nitrogen. Individual cryofreezer monitors are set to tolerances to dictate autofilling with liquid nitrogen through a pipeline fed from the bulk tank, and the entire facility is on generator backup. Access to the biorepository will be restricted to authorized personnel with swipe cards controlled by the building security. Operator access to the LIMS will be password-controlled. Alarmed oxygen sensors are located throughout the biobank in order to alert staff should oxygen levels fall below acceptable concentrations. All staff working or have access to, the biorepository will have anoxia training.

## **7.10. Retrieval of Biospecimens**

When Matrix tubes or GenPlates are retrieved for analysis, an Electronic Work order is generated through the LIMS. The Matrix storage boxes containing the selected tubes are pulled for analysis or transport and loaded directly into a cryocart charged with nitrogen vapour to maintain the biospecimens at similar temperature to that in the cryofreezers. As individual vials are pulled from each box into a secondary box in nitrogen vapour, the individual vials are barcode scanned into the LIMS database, allowing the system to check each vial against the Electronic Work order. As each box is filled, the entire box is barcode scanned to document the location of each cryovial with the storage box. Boxes of cryovials pulled in advance of analysis or shipment will be returned to the long-term nitrogen vapour storage freezers until the day they are thawed for analysis or placed in cryoshippers for shipment. Filter disks from GenPlates are punched out manually or automatically and placed into Matrix tubes. Similarly, barcodes are scanned as described above. GenPlates are returned to the Personal Archive system for continued storage.

## 7.11. Analysis

### 7.11.1. Data Collection Sites

Measurement of hematological parameters is time sensitive. Although a window of 24 hours is acceptable for testing, the CLSA performs this testing at the DCS using one sample of EDTA whole blood. The AcT DIFF Hematology Analyzer from Beckman Coulter (Fullerton, CA) is used to provide a complete blood cell count (e.g., red cell, platelet, neutrophil, and monocyte). This avoids shipping costs and delays as well as provides standardized results across all sites since only one type of instrument will be used. All test data is automatically transferred to the LIMS and be linked to the personal identification number.

### 7.11.2. Biorepository and Bioanalysis Centre (BBC)

The BBC will house a research laboratory dedicated to undertaking detailed sample analysis to answer a variety of research questions. This laboratory is centered on a flexible robotic system designed for custom multiplexing of biomarker assays. The majority of these assays will be antibody based but the system will accommodate any test method that involves liquid handling, incubations, centrifugation, and signal detection by absorbance or fluorescence. Furthermore, DNA, RNA, and membrane preparations will be carried out for other researchers, making this an extremely flexible system. Efficiency will be exercised through measurement of multiple analytes by utilizing several platforms at the same time. In this way, use of each cryovial mitigates refreezing and therefore potential degradation that may occur due to freeze-thaw processes. Although the laboratory is centered on this platform, smaller scale capabilities in the laboratory will be available including cell culture equipment (i.e., incubators, laminar flow hood), flow cytometer, electrophoresis equipment, and a high-pressure liquid chromatography (HPLC) system. The laboratory will incorporate additional pieces of equipment for biomarker analysis as the study progresses.

### 7.11.3. Genetics and Epigenetics Centre (GEC)

The GEC will house a high-density microarray processing centre which will enable the discovery and characterization of potential epigenetic markers associated with aging and complex disease, using both systematic discovery and hypothesis driven experiments. Comprehensive High-throughput Arrays for Quantitative DNA methylation analysis allow for screening and discovery of differences in locus-level genome-wide epigenetic status for individuals. The GEC is a state of the art suite for the quantitative and high dimensional interrogation of the human DNA methylome. Locus difference discoveries can then have accurate quantification and identification of CpG sites involved using a high-throughput system (MassARRAY EpiTYPER, Sequenom). Regions not amenable to this system will be analyzed using pyrosequencing (MD Pyrosequencer, PyroMark) which allows for quantitative DNA methylation analysis of complex genomic regions. As well as epigenetic analysis, this system allows for high-throughput analysis of genetic markers in complex DNA and complements the Real-Time PCR system. This system can be utilized for DNA methylation analysis by PCR amplification of the bisulfite-treated genomic DNA as well as function expression studies for candidate gene promoter and enhancer elements in model animals such as mice. While DNA methylation is the main focus of the GEC, emerging technology for quantitative measurements of histone modification levels in very small samples (Sector 2400 Imager Device, MSD) will also enable the measurements of a number of key histone modifications in peripheral blood samples, which have been shown to change during the aging process. The MiSeq system will be used for exploratory analysis of gene-specific chromatin marks related to aging in primary human samples as well as genetic variation in candidate genes.

*7.11.4. Other*

Discovery and validation of biomarkers may also take place in other research laboratories that have received approval to utilize CLSA biospecimens data. In addition, samples may also be analyzed in clinical laboratories and take advantage of well-validated assays on automated instruments.

## SECTION 8: DATA MANAGEMENT AND SOFTWARE INFRASTRUCTURE

### 8.1. Overview – Data Management

An important priority in the CLSA is to ensure that data are collected efficiently, as well as stored and transmitted securely. Since the CLSA is a multi-site study, the following standard procedures (Sections 8.2 to 8.6 below) are being implemented to promote high-quality attention to data management at each site.

### 8.2. Data Security

The CLSA is committed to respecting personal privacy, safeguarding the confidentiality of personal information in our custody, and ensuring a secure environment for electronic and physical records containing personal information.

The CLSA meets these commitments by:

1. Establishing clear principles and policies for the protection of personal information, emphasizing high standards of organizational, technical and physical security practices and protocols;
2. Communicating privacy protection policies and practices to CLSA staff, affiliates and stakeholders;
3. Restricting access to personal information to those members of the CLSA who have authorized access for research purposes;
4. Submitting research protocols involving use of CLSA data to research ethics boards for review;
5. Ensuring all staff are trained in the principles and practices of personal information protection and requiring all staff to annually commit, in writing, to respect the CLSA's principles, policies and practices in the protection of personal information;
6. Ensuring the CLSA's policies and practices are consistent with national and international standards of privacy protection in health research and legislative requirements.

Two systems of data storage are in use: a manual system and an electronic system. Data stored in the manual system include correspondence-related materials (e.g., address labels, transportable media, signed informed consent forms, and passwords). These are stored in locked filing cabinets in access-controlled environments. Passwords are stored in a separate locked location from other study materials. Data stored on secure servers at the National Coordinating Centre include participant contact information and primary data. Health care registration database data will be stored as per agreements, yet to be developed, with provincial data stewards.

In relation to participant contact information, the CLSA adheres to policies and procedures consistent with the principles described in the CIHR Best Practices for Protecting Privacy in Health Research, Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans and the Canadian Standards Association Privacy Code.

The design of the CLSA data management system includes a centralized secure server on a Virtual Private Network (VPN) where all traffic is Secure Sockets Layer (SSL) encrypted. Workstations are located in access-controlled environments. Only workstations that are authenticated for CLSA use are capable of accessing data. In addition, individuals who wish to access CLSA data using these designated workstations must go through an authentication process before access is permitted.



### **8.3. Data Flow Post-collection**

All collected data, accompanied by unique study identification numbers (de-identified data without name or contact information), is transmitted via VPN to the central server at the NCC. The NCC issues a unique study identification number to each participant after initially receiving the name and contact information. All data linkages with provincial healthcare registration databases will be initiated and overseen by the NCC in collaboration with the Statistical Analysis Centre.

Data transfer between local sites and the NCC is governed by the security protocols specified in the data access agreements that have been signed between McMaster University (home of the NCC) and the universities that host DCS or CATI sites.

### **8.4. Data Transfer and Storage**

Databases and electronic files of collected data are transferred from one location to another in a fully encrypted manner using the VPN. All electronic data are housed on a central server located at the NCC. A complete list of direct identifiers (names, contact information) is stored separately in a master database at the NCC. Only the lead researchers and authorized research staff have the code to link response records to direct identifiers.

All study data, whether electronic (e.g., participant contact information, collected data, data from provincial healthcare registration databases) or paper (e.g., address labels, study introduction letters, transportable electronic media, signed consent forms, passwords), are kept in secure locations that are accessible to authorized personnel only. All computers with access to the VPN employ passwords at both the device and network levels.

DCS interviewers are each assigned a laptop to bring to in-home interviews. All laptop hard drives are password-protected and encrypted to ensure the security of participant data in the event a computer is lost or stolen.

### **8.5. Linkage with Provincial Healthcare Registration Databases**

The NCC or site principal investigators, as required by law, are responsible for applying to the provinces for access to these databases. Data linkage processes will be negotiated between the CLSA (NCC or site principal investigators, depending on provincial requirements) and each province. In cases where provincial healthcare registration database data are not permitted to leave the province of origin, the CLSA will develop data access protocols with the data stewards to facilitate data access for the study.

### **8.6. Data Access**

One of the underlying principles of the CLSA is to provide the research community with the collected data while protecting the privacy and confidentiality of study participants. To this end, the Statistical Analysis Centre coordinates data access, produces locked datasets for each cycle of data collection, and provides statistical support and analytical expertise for internal CLSA analyses. To ensure data quality, the CLSA data curator based at the SAC checks the completeness and accuracy of newly collected data on a regular basis.

The Data and Sample Access Committee (DSAC) reviews all applications for the use of CLSA data (see Appendix G). The DSAC monitors the approved applications on an ongoing basis for progress. Researchers who receive data have an approved time to complete their analyses. If the analyses are not completed in the given time frame, the applicant must either submit a request for a time extension or relinquish the right to use the data. The DSAC, working with the NCC and the SAC, requires

researchers to sign a data sharing agreement that outlines the specific uses of the data and the CLSA's expectations with regard to privacy and confidentiality.

### **8.7. Overview – Software Infrastructure**

Given the scope and complexity of the CLSA's data collection activities, information technology experts employed at the NCC have developed a novel software infrastructure to manage the study's data collection requirements. This infrastructure includes four parts: a participant relationship manager (PRM), computer-assisted telephone interviewing (CATI) software, computer-assisted personal interviewing (CAPI) software, and a central data repository (CDR). Each part, implemented as one or more unique web applications, aggregates new and existing open-source software for specific purposes within the study. Each part is described below.

#### *8.7.1. PRM – Mastodon*

A web service (server) to manage all interactions with participants (including recruitment) and securely store all participants' identifying information, contact information, and consent data. Mastodon provides service to all CATI sites and DCSs.

#### *8.7.2. CATI – Sabretooth and Limesurvey*

Sabretooth is a web service that manages participant data collection for the Tracking cohort, scheduling of interviews, and monitoring of interview progress (e.g., interrupted interviews) until completion. Limesurvey is the software that runs the questionnaires. These applications provide service to all CATI sites.

#### *8.7.3. CAPI – Beartooth and Onyx*

Beartooth is a web service that manages in-home and DCS appointments for all Comprehensive participants. This application provides service to all DCS sites. 'Site' Onyx is a web service that collects data during DCS visits (questionnaire-based data, physical measures, values from medical devices such as DEXA, spirometry, etc.). Onyx 'Laptop' (loaded onto in-home interviewers' laptops) provides questionnaires to collect data during in-home interviews.

#### *8.7.4. Central Data Repository – Opal*

A web service to store data collected from the CATI and CAPI systems described in Sections 8.7.2 and 8.7.3 above. Opal also serves as the mechanism through which data cleaning activities are performed and derived variables are calculated by the data curator. Opal is used to disseminate de-identified data to researchers who are granted access to the CLSA data. Opal provides service to all CATI sites and DCSs.

#### *8.7.5. Laboratory Information Management System (LIMS)*

A LIMS system, not developed by the CLSA yet tailored to the study's needs, is being used at each DCS and at the BBC. It serves as the repository of all data associated with the biospecimens allowing for comprehensive linking of information for efficient quality management and test result handling. The functionalities include detailed tracking of the biospecimens' history from collection, processing, shipping, and storage to their retrieval, dispersal and capturing of analytical data derived from these samples. The laboratory analyzers export data into the LIMS eliminating manual result entry errors. Other features include capture of environmental data from the biospecimens collection rooms and shipping temperatures. Supply inventory, including lot numbers of consumables, are also managed by this system.

## SECTION 9: QUALITY SYSTEM

### 9.1. Staff Training: CLSA Tracking

The NCC provides a three-day CATI training session that is mandatory for CATI Site Coordinators to attend. The objective of this training is to ensure that all CATI Site Coordinators learn the CLSA protocol and receive instruction on how to undertake and monitor all procedures (e.g., shift and sample management) related to the CLSA Tracking. The training is standardized to ensure that all sites are performing procedures in a standardized manner. The CATI Site Coordinators are responsible for training their local staff on the subject matter covered during the training session.

The NCC has developed a Training Manual describing the administration of standardized calling scripts, interview scripts, and questionnaires. Staff at the NCC has also developed standard operating procedures to cover data storage, security breaches, and other issues related to the daily operations of the CLSA. These procedures are disseminated during training sessions. Additionally, training videos that portray mock interviews have been developed to assist in training.

Each site holds staff debriefing sessions on a regular basis to assess the effectiveness of training and determine the need for supplementary training. Site managers/coordinators routinely review recruitment statistics (e.g., number of persons recruited out of total number contacted) and throughput statistics (e.g., number of successfully completed interviews) to assess whether deficiencies exist that might require additional training or revisions to training procedures. CATI managers also monitor live telephone interviews on a random basis to ensure interviewers are maintaining a standardized approach to interviewing.

### 9.2. Staff Training: CLSA Comprehensive

All newly hired DCS Coordinators are required to attend a three-day mandatory training session at the NCC. The objective of this training session is to ensure that the DCS Coordinators learn the CLSA protocol and receive instruction on how to undertake and monitor all Comprehensive procedures (in-home interview and DCS visit). The DCS Coordinator training is standardized to ensure that all sites are performing study procedures in a standardized fashion. The DCS Coordinators are responsible for training their local DCS and in-home staff on all of the subject matter covered during the training session.

The NCC has developed standard operating procedures to govern all facets of dealing with study participants during DCS visits. These procedures govern welcoming and registering participants, administering physical and questionnaire-based tests, and collecting blood and urine samples. Standard operating procedures are supplemented with a DCS Training Manual to promote standardized participant assessments.

CATI and DCS staff is encouraged to discuss issues that arise during the conduct of interviews and during the performance of physical or clinical tests. These issues could include problems with question interpretation or the adequacy of response options, as well as difficulties with performing tests in accordance with standard operating procedures. Staff bring these issues to the attention of their immediate supervisors, who contact the NCC for guidance. Scientists and operational staff at the NCC assess the issues, determine corrective measures (if needed), and issue bulletins to the sites. Standard operating procedures and questionnaires are revised accordingly. A supplemental questionnaire-training manual also exists to help staff better interpret the meaning and applicability of certain questions. This supplemental manual is updated regularly in response to queries from staff.

The CLSA uses videoconferencing technology to allow all CATI and DCS personnel to receive simultaneous, standardized training updates. Videoconferencing is used to update CLSA personnel in the event additional training is required in response to revised study procedures.

### **9.3 Quality Assurance**

CLSA Comprehensive quality assurance (QA) procedures ensure the standardized collection and documentation of accurate, reliable data. The goal is to minimize intra- and inter-examiner variability, reduce error, maintain participant satisfaction and safety, and protect privacy and confidentiality at each DCS. The purpose of the QA plan is to describe the practices in place for monitoring the quality of our physical measurements, cognitive testing, laboratory sampling, and staff performance. The QA plan also contains the quality assurance procedures for evaluating the performance of the 11 DCS. This document provides specific directions for the minimum frequency and timing of local site monitoring, as well as guidelines for expert input and monitoring visits by the NCC's QA staff. The QA plan describes participating staff responsibilities, equipment checks, monitoring visit checklists, QA evaluation levels, and QA reporting procedures.

The CLSA Tracking QA plan outlines standard quality assurance practices for monitoring interviewers during data collection and evaluating the performance of interviewers and CATI Site Supervisors. Specific instructions include how to monitor interviewers and the required frequency of this monitoring.

CATI Site Coordinators monitor approximately 10% of all live interviews to ensure that interviewers avoid lead participants, read questions and response options as written, do not skip questions or response options, and accurately code responses. This monitoring identifies situations where interviewers require coaching for potentially problematic questions.

To assess the quality of the cognitive scoring data, the NCC checks and verifies approximately 5% of the data from each CATI site. If any issues are noted, then further review of the data may occur and further training may be provided to the sites.

### **9.4. Electronic Data Collection and Capture**

To uphold the validity of participant data, all questionnaires are programmed into, and administered using, the CATI and CAPI software. Questionnaire responses and data from clinical tests such as DXA or spirometry are exported directly into the CLSA database. For physical and anthropometric tests, standard operating procedures dictate how staff manually enters results into the CLSA database.

Staff from the BBC attend 'Train the Trainer' sessions to instruct DCS coordinators in the proper procedures surrounding biospecimens. BBC staff has also developed standard operating procedures for specimen collection and handling.

### **9.5. Equipment Maintenance and Calibration**

DCS coordinators ensure strict adherence to manufacturers' guidelines for equipment maintenance and calibration. The BBC laboratory manager has the same responsibility at the BBC. NCC and BBC staff has developed standard operating procedures to explain maintenance and calibration procedures and schedules. Logbooks are maintained to verify that equipment has been maintained and calibrated on schedule.

Signed invoices for maintenance operations are maintained in a hard copy file folder and scanned into an electronic folder. All equipment maintenance performed by study staff is recorded in the logbook and any documentation arising from in-house maintenance is stored in the same manner as the invoices.

### **9.6. Data Cleaning**

The SAC checks the completeness and accuracy of newly collected data at regular intervals. Raw, de-identified data are imported via the CLSA's VPN into an open-source software application called 'Opal', which can be used to summarize these data. The SAC examines the data summaries for anomalies (e.g., missing data, improper skip patterns, invalid open-text entries). A data cleaning committee considers the best course of action to correct any anomaly (e.g., contact sites to follow-up with participants regarding missing data, alter question skip patterns, revise open-text guidelines, provide supplemental staff training to prevent data collection errors).

In Opal, the SAC programs algorithms to correct anomalies in existing data. As well, another set of algorithms is programmed to calculate derived variables (e.g., Body Mass Index from height and weight). Thus, raw data are left untouched and Opal is used to produce cleaned datasets.

### **9.7. Quality Control**

The CLSA includes a quality control team composed of NCC (operations manager, associate scientific director) and SAC staff (centre director, statistician). This team developed the procedures described in Section 9.5 above and works in conjunction with the data cleaning committee to address the CLSA's data quality needs.

A series of automatically generated reports are distributed on a regular basis to the CATI manager and DCS coordinator at the NCC, as well as to the senior management team, to permit the monitoring of participant recruitment, interview bookings, and completions, and DCS visit bookings and completions.

### **9.8. Evaluation of Study Process**

The CLSA includes a system of reporting and solving challenges that may arise during data collection or analysis. The CLSA has created committees to develop, oversee, and evaluate the study process (Appendix J). The NCC disseminates 'incident reports' and follow-up directives to study sites. CATI managers and DCS coordinators ensure that staff are familiar with these reports and any resulting corrective action.

## **SECTION 10: GOVERNANCE AND STUDY MANAGEMENT**

### **10.1. Overview**

The duration and scope of the CLSA necessitate a carefully crafted governance structure and management plan to ensure scientific excellence, as well as the long-term sustainability of the project. The CLSA governance structure is designed to provide robust management that allows for the potential for modification and growth over time. The model allows for facile management of scientific and executive succession strategies, accommodating future extensions of the project and the incorporation of additional funders and stakeholders.

The management structure to oversee the implementation, operation, functionality, and sustainability is integrated within the governance framework to ensure that the scientific vision of the CLSA is achieved. The science of the CLSA and its supporting infrastructure is administered through the Scientific Management Team (SMT), the Operations Committee (OC), and the Data and Sample Access Committee (DSAC). Key personnel are responsible for enabling the work of the committees.

The SMT is the principal governing body of the CLSA and is supported in its work by the CLSA Advisory Council (AC) and the International Scientific Advisory Board (ISAB). External oversight for the CLSA is provided by the CIHR and the Advisory Committee on Ethical, Legal, and Social Issues (ELSI). The CLSA management structure is described in Appendix J.

Site investigators are responsible for local CATI and DCS operations. Expert working groups are responsible for the development of the CLSA content.

### **10.2. CATI Sites**

The CLSA has four regional CATI sites (Dalhousie University, Université de Sherbrooke, University of Manitoba, and University of Victoria). Université de Sherbrooke is responsible for all French interviews. The English interviews are distributed geographically among the four CATI sites. The CATI sites use open source software (see section 8.7.2) and a voice over internet protocol (VoIP) to conduct interviews, specifically tailored to meet the study needs and privacy requirements of the CLSA. Software such as Limesurvey has comprehensive logic instructions to guide respondents through the correct question sequence and skip patterns, and can be programmed to check the validity of answers given in real-time. This software supports both English and French surveys. To ensure standardization, software programming is done centrally at the NCC. Pilot testing of scripts and questionnaires is conducted at all CATI sites prior to data collection.

### **10.3. Data Collection Sites**

There are 11 DCS spread across the country: Victoria, Vancouver, Surrey, Calgary, Winnipeg, Hamilton, Ottawa, Montréal, Sherbrooke, Halifax, and St. John's. The Montréal and Sherbrooke sites are equipped to serve participants in English or French, while the other nine sites serve participants in English.

To ensure a standardized data collection process prior to full operationalization, the Montréal and Hamilton DCS were established as the test sites to pilot the data collection process and standard operating procedures. The selection of Montréal as a test DCS allowed data collection procedures to be verified in French.

## SECTION 11: DISSEMINATION

Strategies for the dissemination of research results must be developed to meet the needs of a variety of end users (e.g., the public, health service providers, managers, researchers, and policy makers). Nevertheless, the key to bridging transferable research with community action will be addressed through knowledge transfer and exchange. It is essential that communities involved in the care, prevention and development of public policy for the aging population receive support in the interpretation and use of research results, ultimately to improve the health of all Canadians.

The Knowledge Translation and Communications Committee (KTCC) is the primary body responsible for initiating and facilitating knowledge translation and communications activities that support the objectives of the CLSA. The KTCC is responsible for developing a framework and action plan that will involve recommendations on the following knowledge translation activities:

- 1) Presenting research findings at national and international conferences and publishing the findings in peer-reviewed scientific and clinical journals;
- 2) Circulating lay summaries of research findings directly to clinicians, governments (e.g., ministries of health, public health departments), health charities, CIHR institutes, and citizens' advocacy organizations;
- 3) Posting all disseminated material such as research findings, working papers, reports, published journal articles, and lay summaries on the CLSA website and its social media platforms; and
- 4) Producing regular newsletters and publications for all stakeholders to describe the study's progress and highlight new and important findings;
- 5) Engaging in community outreach initiatives, such as speaking events and seminars (including CIHR Café Scientifique), to promote the dissemination and exchange of health research evidence.

## **SECTION 12: THE STUDY TEAM**

### **12.1. A Collaborative Approach**

The multidisciplinary nature of the CLSA allows for and requires rich collaborations and capacity building both across and between multidisciplinary researchers, practitioners, and policy makers. The CLSA collaboration began with a 2001 symposium — From Cell to Society — in Aylmer, Quebec, where over 80 researchers from 50 institutions across Canada agreed on the need for a new generation of longitudinal studies to support a research program in aging.

The CLSA lead scientific team brings together a diverse group of researchers with a wide range of expertise, including genetics, biochemistry, immunology, medicine, geriatrics and gerontology, sociology, psychology, nursing, pharmacy, biology, rehabilitation, epidemiology, health services, computer science, medical anthropology, population health, nutrition, economics, and biostatistics. All of the team members have published their research findings in leading scientific journals, held national and international peer-reviewed grants, and have had considerable experience in translating their findings into policy.

### **12.2. CLSA Team**

The CLSA team is directed by lead principal investigator, Dr. Parminder Raina of McMaster University, and two co-principal investigators, Drs. Christina Wolfson of McGill University and Susan Kirkland of Dalhousie University. The CLSA team includes a network of researchers who lead the data collection and computer assisted telephone interview sites and enabling units. The names and affiliations of each of our site investigators and the leads of enabling units are available on [www.clsa-elcv.ca](http://www.clsa-elcv.ca). In addition, CLSA includes a network of researchers across Canada who participate in development of the CLSA scientific content and methods via the expert working groups (see [www.clsa-elcv.ca](http://www.clsa-elcv.ca)).



## **SECTION 13: TRAINING, COLLABORATIONS, AND PARTNERSHIPS**

### **13.1. Overview**

The CLSA research platform will provide a remarkable opportunity to train multidisciplinary researchers in the field of aging. To ensure the ongoing success of the CLSA, the study team will foster relationships and collaborations with stakeholders at the national and international levels.

### **13.2. Training of Highly Qualified Personnel**

To ensure that the challenges faced by an aging population remain a research priority in Canada, there is an urgent need to invest in the next generation of researchers. Strategic approaches are required to foster training in an environment of innovation and research excellence, stimulating a culture of interdisciplinary research that integrates the biological, clinical, and population sciences. The CLSA will provide a fertile training environment to foster and sustain collaboration among trainees, researchers, health practitioners, policy makers, and their respective institutions across Canada and internationally. This will advance the interdisciplinary science of aging in Canada.

Currently, the demand for highly qualified personnel (HQP) in Canada vastly outstrips supply, thereby creating an urgent need for training. The true integration of the biological sciences, and in particular, genetics, with the social sciences has yet to be achieved. It is also widely recognized within the Canadian research community that Canada has an inadequate supply of quantitative (biostatistics) researchers to support the national health research agenda. The CLSA is ideally suited to build capacity to address these issues.

The Training and Research Capacity Committee (TRCC) is responsible for promoting the training vision of the CLSA and building research capacity in interdisciplinary, longitudinal approaches to the study of aging, via the development and implementation of educational policies and programs that utilize the infrastructure. A key role of the TRCC is to liaise with existing institutional programs in aging and population health, and to integrate the training within the infrastructure platform. The TRCC seeks to engage new researchers in the work of the CLSA to ensure an innovative, interdisciplinary training environment for future Canadian scientists. Members are selected from the pool of CLSA investigators, based on their deep commitment to training and mentoring and their relevant expertise and interest, with an aim to achieve multidisciplinary and regional representation.

The mandate of the Training and Research Capacity Committee (TRCC) is to: 1) advance training and research capacity within the context of the CLSA; 2) to bring new trainees and researchers into the CLSA; and 3) to raise awareness of the potential for trainees and researchers within the CLSA. The needs and outputs for training within the CLSA differ according to its stage of development. In the early stages, prior to the initiation of CLSA data collection, emphasis was placed on providing opportunities for trainees that could inform and prepare researchers for the CLSA using relevant technologies, methodologies or other datasets. As the data collection tools were developed, the emphasis shifted to creating awareness of the instruments used and the potential for posing cross-disciplinary, longitudinal research questions that utilize the CLSA to its fullest potential. As we approach the release of the first wave of CLSA data, the TRCC plans to develop a series of training modules that encompass an orientation in Social Sciences/Humanities, Epidemiology/Biostatistics, Basic Sciences/Genetics, Clinical/Health Outcomes. Training modules will be developed to: 1) understand and be aware of CLSA's main objectives and methods of data collection; 2) get basic knowledge of how CLSA's database(s) are built and what variables they contain; 3) get knowledge on how to obtain data from CLSA; 4) get knowledge of possible additional opportunities (blood dosage from stored samples,

secondary studies on subsamples, intervention studies, etc.); 5) develop ideas of possible interdisciplinary research (in respect to their own area of research) within the course of CLSA; 6) demonstrate basic skills for the management and analyses of large datasets (with respect to their own area of research). By completing the series of modules, trainees from a wide range of programs and universities can acquire a CLSA Certificate that complements the requirements of their respective programs. These modules will be used as the foundation for a dedicated CLSA Training Program in the future. Ultimately, our aim is to support undergraduate, graduate, postdoctoral trainees and new researchers in longitudinal, transdisciplinary research on healthy and successful aging using data, samples and infrastructure of the CLSA.

The CLSA will seek funding from granting agencies such as CIHR to train HQP. The receipt of infrastructure funding from the Canada Foundation for Innovation was of paramount importance in establishing the research platform upon which to base training initiatives.

### **13.3. Collaborations and Partnerships**

The CLSA has been a highly collaborative endeavour from the outset and teamwork has been at the heart of the development of the CLSA. The core research team is a dynamic and highly productive group of national and international leaders in the field of aging who all have ongoing collaborations with national and international research teams and these collaborations will be further enhanced by the CLSA. The lead and co-principal investigators have also developed strategic collaborations and associations with national and international researchers and teams in the field of aging and longitudinal studies. These collaborations will achieve three major objectives: 1) the exchange of techniques, skills and expertise relevant to the study of aging in Canada; 2) the enhancement and advancement of opportunities for scientific gains to be made, particularly with respect to areas which require large numbers of ethnically diverse groups, such as population genomics, and the study of gene-environment interactions; and 3) the sharing of the design, conduct, content or study measures with major studies in anticipation of harmonizing information to allow for international comparisons.

#### *13.3.1. National Collaborations*

On the Canadian front, the principal investigators have had extensive engagement with the lead researchers of past and present longitudinal studies on aging: Dr. Ian McDowell of the Canadian Study of Health and Aging (CSHA); the late Dr. Betty Havens of the Longitudinal Study of Aging in Manitoba (AIM); and Dr. Robert Tate of the Manitoba Follow-up Study (MFUS). These interactions have been instrumental in providing insight into the logistical and, in particular, the infrastructure challenges of conducting longitudinal research over an extended period in Canada. Each of the principal investigators also brings to the CLSA a wealth of experience and the potential to collaborate with overlapping networks from their involvement in national consortia and projects such as the Canadian Multicentre Osteoporosis Study (CaMos), the Canadian Health Measures Survey (CHMS), CARTaGENE, and other cohorts such as the Canadian Partnership for Tomorrow (CPT). The infrastructure allows for greater intersection and opportunities for collaborative partnerships to further develop with these teams.

#### *13.3.2. International Collaborations*

Over the last number of years, the principal investigators have been in contact with the lead researchers of renowned international longitudinal studies and established the potential for ongoing collaborative relationships. These contacts include Dr. Diana Kuh of the British 1946 Birth Cohort Study, Dr. Alfredo Morabia of the Geneva “Bus Santé Programme”, Dr. Brigitte Santos-Eggiman of the Lausanne Frailty Study, Drs. James Nazroo from the English Longitudinal Study on Aging (ELSA), Dr. Avan Aihie Sayer from the Hertfordshire Cohort Study, Dr. Dorly Deeg from the Longitudinal Aging Study

Amsterdam (LASA), Luigi Ferrucci of the Italian InChianti study and the Baltimore Longitudinal Study on Aging, Dr. Marcel Goldberg from the Cohorte Constances in France and Dr. David Weir of the Health and Retirement Study in the US. Moreover, in the feasibility phase, we conducted telephone interviews with the principal investigators and project coordinators of fifteen key longitudinal studies in Australia, Canada, England, Netherlands, Sweden, and the United States. These study groups have expressed keen interest in the CLSA and have shared protocols concerning study content, funding sources, governance, personnel, data management and dissemination strategies.

Discussions have begun to explore the possibility of harmonizing elements of the study content across ongoing and planned international longitudinal studies of aging. The Lead Investigators are participating in collaborations with international longitudinal studies as well as in applications to different funding agencies for collaboration with other international longitudinal studies to harmonize research findings. This strategy will allow the CLSA to conduct international comparisons, exchange expertise, and extend international collaborations. The CLSA principal investigators have also been invited as participants in several working meetings of the P3G, an international consortium to promote collaboration between researchers in the field of population genomics and have begun a working relationship.

#### *13.3.3. Policy and Decision Maker Collaborations*

Our collaborative partners, and eventual users of the research results, include key federal and provincial agencies, most notably, Statistics Canada, Health Canada, Veterans Affairs Canada, and the Public Health Agency of Canada. In particular, we have already collaborated closely with Statistics Canada and Health Canada to develop the content for the Canadian Community Health Survey on Healthy Aging that is also serving as a recruitment vehicle for the CLSA. We have worked intensively with Statistics Canada to chart new territory in terms of data sharing, and this has culminated in the signing of a Memorandum of Understanding between Statistics Canada and the three lead institutions (McMaster, Dalhousie, and McGill). This collaboration is the enactment of our shared vision for a Canadian longitudinal study that capitalizes on strengths and opportunities to address the issues facing Canada's aging population. The CLSA team has formed, and will continue to form, strategic alliances, and collaborations with provincial agencies to support the operations of the CLSA initiative together with federal partners. For example, during its development, the CLSA was identified as a strategic initiative by the Geriatric Research Network of the Fonds de Recherche en Sante du Quebec (FRSQ), and feasibility studies have been supported by the BC Network for Aging Research (BCNAR).

We have successfully worked with provincial Ministries of Health and Health Authorities/Regions of all provinces across the country to garner support and ensure that provincial policy needs will be met within the CLSA. Through these collaborative relationships, we have successfully started our recruitment for the Tracking and Comprehensive cohorts using provincial health registries. In addition, collaborative relationships have been formed with privacy commissioners in several provinces. These collaborations are particularly important for the future of research in Canada in which linkage to databases under provincial jurisdictions are planned.

#### *13.3.4. Plans to Strengthen Partnerships*

There are currently a number of other large-scale initiatives under development in Canada that we have explored potential links with, and will continue to build collaborative bridges with, as they progress. In particular, we will further explore collaborative avenues with our colleagues across the country involved in the recently established Canadian Partnership Against Cancer (CPAC) cohorts, a series of five regional cohorts to investigate the development of cancer. We have already held meetings with this group and are sharing knowledge on IT, data access policies, and standard operating procedures.

With respect to the health charities, the principal investigators have explored partnership opportunities alone and in conjunction with CIHR's Institute of Aging. This has resulted in considerable support from a number of the health charities, including the Canadian Neurological Society, the Parkinson Society of Canada, the MS Society of Canada, the Heart and Stroke Foundation and the recently formed Neurological Health Charities Canada. The CLSA is connecting with a number of additional charities through the Health Charities Coalition of Canada (HCCC) and is developing a health charities consortium to support the CLSA.

Partnerships with a wide range of private companies such as pharmaceutical, diagnostic, and medical supply companies, equipment suppliers, health information and financial institutions and private foundations are being pursued now. A number of meetings have been held resulting in various partnership commitments.

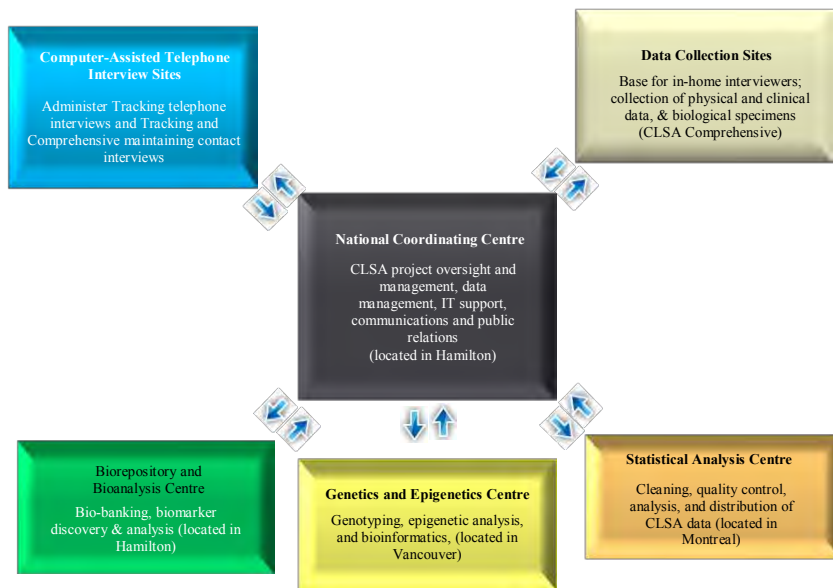
Finally, we have a partnership and communication strategy in place to structure partnership development around the CLSA implementation stages. Our established infrastructure is vital in maintaining existing partnerships and securing new partners. The network of fully functional physical research environments across the country will provide an ongoing legacy for interdisciplinary and translational research activity on aging well into the future.

### SECTION 14: CLSA INFRASTRUCTURE

The availability of a dedicated infrastructure to conduct state-of-the-art, interdisciplinary, population-based research in Canada is necessary to promote the long-term success of initiatives such as the CLSA. This infrastructure must be broad enough to ensure efficient and sustained study operation and management. The infrastructure must also include a national capacity to collect and link primary data, securely store biological and clinical samples, and securely store large amounts of alphanumeric and radiographic image data.

The Government of Canada, through the Canadian Foundation for Innovation, funded this infrastructure in June 2009. The infrastructure, which will be fully in place by the end of 2013, includes the National Coordinating Centre (NCC), a Biorepository and Bioanalysis Centre (BBC), four CATI sites, Genetics and Epigenetics Centre (GEC), a Statistical Analysis Centre (SAC), and 11 DCS (Figure 14.1). Each of these units is equipped with the specialized equipment needed to capture, store and analyze data at a level not currently available in Canada.

**Figure 14.1 Equipment and Infrastructure Supporting CLSA**



The NCC, BBC, all four CATI sites, GEC, SAC, and 10 DCS are currently functional. The Vancouver will open by the end of 2013.

The roles of these infrastructure components are described below.

- National Coordinating Centre (NCC): The NCC, based at McMaster University, is responsible for the overall management of the CLSA. The NCC manages the recruitment of CLSA participants, leads data collection operations, develops standard operating procedures and protocols, provides staff training, and plays a central role in data management (e.g., the NCC initiates all data linkages with provincial healthcare registration databases). The NCC also provides overall management of the DCS.
- Computer-Assisted Telephone Interviewing Centre (CATI): The CATI centre based at Dalhousie University shares responsibility for overseeing the operation of all CATI sites in collaboration with the NCC. CATI sites are responsible for conducting the main-wave interviews for the CLSA Tracking and the mid-wave (MC) interviews for the CLSA Tracking and Comprehensive.
- Statistical Analysis Centre (SAC): The SAC, based at McGill University, is the analytic nexus of the CLSA and works closely with the NCC to provide secure data storage, user management and statistical collaboration to CLSA researchers and other users of the CLSA research data platform. The SAC only has access to de-identified data and provides secure data storage, produces a cleaned, linkable, locked dataset for each cycle of data collection. The SAC also provides quality control checks of collected data on a regular basis.
- Data Collection Sites: Each DCS, led by a site principal investigator, is responsible for conducting the physical assessments, collecting biospecimens, and administering questionnaire-based assessments (at the in-home interview and during the DCS visit) for 3,000\* participants during each three-year wave of the study. DCS interviewers also make initial recruitment telephone calls to potential Comprehensive participants. (\*In British Columbia, the Vancouver and Surrey DCS are responsible for 1,500 participants during each wave.)
- Biorepository and Bioanalysis Centre (BBC): The BBC is located in Hamilton and its responsibilities include biobanking, biomarker discovery, and analysis.
- Genetics and Epigenetics Centre (GEC): The GEC is located in Vancouver at the Centre for Molecular Medicine and Therapeutics at the Children's and Women's Hospital site. The GEC is closely affiliated with the Brain Research Centre. The GEC is responsible for genotyping, epigenetic analyses, and bioinformatics using unbiased microarray-based approaches to measure the genome in subsets of CLSA subjects over time.

## SECTION 15: ETHICAL CONSIDERATIONS

### 15.1. Overview

There are several numerous challenges to studying the multi-faceted nature of aging among individuals over a long period. For example, the cognitive decline of some older participants may pose challenges for maintaining informed consent. As well, because the CLSA will be a longitudinal study of at least 20 years duration, new and yet undeveloped tests and analyses cannot be specified at the time of recruitment. To set the stage to address these challenges, the Canadian Institutes of Health Research (CIHR) established a committee to address the ethical issues related to CLSA. The roles and responsibilities of the ELSI Committee are to:

- Identify key ethical legal and social issues facing the implementation of the CLSA;
- Guide the development of policies and procedures regarding the ethical, legal, and social issues relevant to the CLSA; and
- Ensure that the objectives, activities, and outcomes of the CLSA are transparent to participants and external reviewers at all times.

The ELSI committee has assisted the CLSA investigators in the development of the consent process and the information package. The committee also commissioned several papers that informed the ELSI discussions. Ethical challenges associated with the CLSA are evaluated on a continuing basis by the CLSA researchers and ELSI. The conduct of the CLSA conforms to the ethical and legal guidelines that have been developed in conjunction with this committee. Ethical aspects of CLSA are a subject of ongoing collaboration and consultation with ELSI. Key areas of ongoing consultation include the routine return of individual test results to participants, the return of additional test results to participants, the use of advance directives in research, the process for using proxies and informants in the case of cognitive decline, and the process for participant withdrawal from the study. The ELSI terms of reference is contained in Appendix K.

### 15.2 Research Ethics Board Approval

Initial efforts to obtain institutional ethics approvals were characterized by sequential submissions across ethics boards in seven different provinces. While successful, there were two areas we hoped to improve. They were: 1) The length of time it took to complete the full sequence of ethics review, (7 months), and 2) Each Ethics Board focused on different aspects of the protocol and its associated appendices resulting in differences in the documentation across the sites. The latter was of particular concern for printing and assembling inter-jurisdictional participant information package.

In the fall of 2009, Hamilton Health Sciences/Faculty of Health Sciences, McMaster University, under the leadership of Dr. Jack Holland (Chair), agreed to explore the possibility of creating a forum for ethics boards whereby those asked to review and approve applications from the Canadian Longitudinal Study on Aging (CLSA) could provide a single unified response to CLSA applications.

A process was initiated in January 2010 related to the approval of CLSA amendments to the Tracking Cohort Protocol. Among the ethics boards, who had previously approved the full Tracking Protocol and who participated in the collaborative amendment approval process, were: Dalhousie University, McGill University, McMaster University, Memorial University of Newfoundland, Université de Sherbrooke, University of Manitoba, and University of Victoria.

The CLSA submitted a full-integrated protocol, including the Tracking and Comprehensive Cohort protocols in July 2010. In addition to the universities identified above, the full integrated protocol was

also be submitted to: Simon Fraser University, Vancouver Island Health Authority, University of Ottawa, University of British Columbia, and the Prince Edward Island REB. The University of Calgary opted not to participate in the collaborative REB review and receives separate REB submissions.

Since the approval of the integrated protocol, amendments to the integrated protocol are submitted yearly through the collaborative REB process and to the University of Calgary REB.

### **15.3 Risks to Participants**

Since the CLSA is a population-based, observational research, the study is of low physical risk to the participants. One possible risk to participants relates to the risk of a breach of confidentiality. To minimize this risk, all data related to the CLSA will be stored and used in a de-identifiable format and will be handled in strict accordance with the Tri-Council Policy Statement, the data privacy guidelines of each of the Canadian provinces and territories, and guidelines established by the ELSI Committee. The CLSA Privacy Policy is posted on the CLSA website and is included in Appendix L. Researchers will only be given access to de-identifiable data, i.e., data from which all identifiers have been permanently stripped so that there is no reasonable potential for any organization or person to identify a specific individual. The CLSA will undertake linkage with nominative information only under specific circumstances (for instance, to add new information about a participant) and nominative information will be kept under strict security measures by the NCC.



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**SECTION 17: GLOSSARY**

<b>Abbreviation</b>	<b>Description</b>
ACD	Acid Citrate Dextrose
AD	Alzheimer's Disease
ADL	Activities of Daily Living
ATS	American Thoracic Society
AUC	Area under the curve
BBC	Biorepository and Bioanalysis Centre
BCS	Biospecimens Collection Station
BMD	bone mineral density
CAO	chronic airflow obstruction
CAPI	Computer Assisted Personal interview
CATI	Computer Assisted Telephone Interview
CCHS	Canadian Community Health Survey
CES-D	Center for Epidemiologic Studies – Depression
CES-D10	Center for Epidemiologic Studies Short Depression Scale
CHARM	Comprehensive High-throughput Arrays for Relative Methylation
CHMS	Canadian Health Measures Survey
c-IMT	Carotid intima-media thickness
CLSA	Canadian Longitudinal Study on Aging
COPD	chronic obstructive pulmonary disease
CPT	cell preparation tube
CRCTL	Clinical Research and Clinical Trials Laboratory
CRT	Choice Reaction Time
CTFPHC	Canadian Task Force on Preventive Health Care
CTUMS	Canadian Tobacco Use Monitoring Survey
CVE	cerebrovascular event
DSAC	Data and Sample Access Committee
DBP	diastolic blood pressure
DCS	Data Collection Site(s)
DIN	Drug Identification Number
DMSO	Dimethyl sulfoxide
DNA	Deoxyribonucleic acid
DXA	dual energy x-ray absorptiometry
ECG	electrocardiogram
EDTA	Ethylenediaminetetra acetic acid
ELISA	Enzyme-linked immunosorbent assay
ELSA	English Longitudinal Study of Aging
EPESE	Established Populations for Epidemiologic Studies of the Elderly
ERS	European Respiratory Society
FBS	fasting blood sugar
FCM	Federation of Canadian Municipalities
FDA	Food and Drug Administration
FDT	Frequency Doubling Technology

<b>Abbreviation</b>	<b>Description</b>
FEV	forced expiratory volume
FFQ	Full Food Frequency Questionnaire
FVC	forced vital capacity
GEC	Genetic and Epigenetic Centre
GSS	General Social Survey
HRS	Health Retirement Survey
IADL	Independent Activities of Daily Living
ICC	Inter-Class Correlation
IOM	Institute of Medicine
IOP	Intraocular Pressure
K10/K6	Kessler Psychological Distress Scale
LIMS	Laboratory Information Management System
LSA	Life Span Assessment
MAT	Mental Alternation Test
MMSE	Mini-Mental State Examination
MOU	Memorandum of Understanding
NCC	National Coordinating Centre
NHIS	National Health Institutes Survey
NPHS	National Population Health Survey
NSMHWB	Australian National Survey of Mental Health and Well-Being
OA	Osteoarthritis
OARS	Older Americans Resources and Services
OSIRIS	Osteoporosis Index of Risk
PASE	Physical Activity Scale for the Elderly
PC-PTSD	Primary Care Posttraumatic Stress Disorder
PCR	polymerase chain reaction
PD	Parkinson's Disease
PMT	Prospective Memory Test
PTA	pure tone audiometer
PTSD	Posttraumatic Stress Disorder
PTT	pure-tone threshold
QCT	Quantitative Computed Tomography
QVSFS	Questionnaire for Verifying Stroke-Free status
RAVLT	Rey Auditory Verbal Learning Test
RNA	Ribonucleic acid
RT	Reaction Times
SBP	systolic blood pressure
SDQ	Short Diet Questionnaire
SES	Socioeconomic status
SHARE	Survey of Health, Aging and Retirement in Europe
SNP	single-nucleotide polymorphism
SSL	secure sockets layer
T4	thyroxine
TENFLEX	Tenacious Goal Pursuit and Flexible Goal Adjustment Scales

<b>Abbreviation</b>	<b>Description</b>
TIA	Transient Ischemic Attack
TSH	Thyroid Stimulating Hormone
TUG	Timed up and go
U.S.	United States
VPN	Virtual Private Network
WHAS	Women's Health and Aging Study