STUDY PROTOCOL

CARRS

Center for c**A**rdiometabolic **R**isk Reduction in **S**outh Asia

SURVEILLANCE STUDY

Study protocol: Version 1.~~2~~ 3 | ~~July 2012~~Nov 2012

Center for cArdiometabolic Risk Reduction in South Asia (CARRS):

Surveillance Study

Study Protocol

Version 1.~~2~~3, ~~July 2012~~Nov 2012

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List of Abbreviation

AIIMS	All India Institute of Medical Sciences
AKU	Aga Khan University
ApoA/B	Apolipoproteins A & B
BMI	Body Mass Index
BP	Blood Pressure
BRFSS	Behavioural Risk Factor Surveillance System
CAP	College of American Pathologists
COE-CARRS	Center of excellence- Center for Cardiometabolic Risk Reduction in South Asia
CDC	Centers for Disease Control and Prevention
CEB	Census Enumeration Blocks
CHD	Coronary Heart Disease
CHF	Congestive Heart Failure
CKD	Chronic Kidney Failure
CMD	Cardiometabolic Diseases
CUPS	Chennai Urban Population Study
CURES	Chennai Urban Rural Epidemiology Study
CVD	Cardiovascular Disease
DM	Diabetes Mellitus
DMC	Delhi Municipal Corporation
EQ-5D	European Quality of Life 5
FPG	Fasting Plasma Glucose
HbA1c	Glycated Hemoglobin
HDL	High Density Lipoprotein
HINTS	Health Information National Trends Study
HTN	Hypertension
IDSP	Integrated Diseases Surveillance Project
IRB	Institutional Review Board
KAP	Knowledge, Attitudes, and Perceptions
LDL	Low Density Lipoprotein
LMCI	Low- and Middle-Income Countries
MDRF	Madras Diabetes Research Foundation
MI	Myocardial Infarction
MONICA	Multinational MONItoring of trends and determinants in CArdiovascular disease
MOP	Manual Of Operations
NABL	National Accreditation Board for testing and calibration Laboratories
NCCD	National Center for Chronic Diseases
NCD	Non Communicable Diseases
NDMC	New Delhi Municipal Corporation
NHLBI	National Heart, Lung and Blood Institute
NIH	National Institutes of Health
NPDCS	National Program for Prevention and Control of Diabetes, CVD and Stroke

PHFI	Public Health Foundation of India
PI	Principal Investigators
PVD	Peripheral Vascular Disease
QME	Quality Monitoring and Evaluation
SOP	Standard Operating Procedures
TG	Triglycerides
UA	Unstable Angina
VLDL	Very Low Density Lipoprotein
WHO	World Health Organization

I. Background

I.i. Cardio-metabolic diseases (CMD)

Cardio-metabolic diseases include diabetes mellitus (DM), cardiovascular disease (CVD), kidney disease and common risk factors that underlie these conditions such as central obesity, insulin resistance, glucose intolerance, dyslipidemia, and hypertension. CMD are a growing public health problem worldwide which is gradually becoming a pandemic.[1] They are among the top ten most costly diseases, but they have the advantage of being predictable through identification of distal and intermediate risk factors and also preventable through changes in lifestyle particularly through healthy eating habits and regular physical activity.[1]

I.ii. Cardio-metabolic disease burden

It is estimated that coronary heart disease (CHD), cerebrovascular disease, and diabetes together account for 30% of global mortality and 80% of these deaths occur in low- and middle-income countries (LMIC).[2-4] Diabetes commonly co-exists with obesity (both generalised and central), hypertension,[5] and lipid abnormalities (elevated triglycerides, low HDL-cholesterol, abnormal LDL-cholesterol sub-fractions) and is a central feature accelerating athero-thrombotic cardiovascular disease (CVD), it is the leading cause of adult-onset blindness, non-traumatic amputations and kidney failure worldwide. The addition of these inter-related risk factors and co-morbidities results in a multiplicative, rather than additive, amplification of risk of severe outcomes (such as CVD events, amputation, etc.) and mortality.[6]

In people of South Asian origin, diabetes, cardio-metabolic risk factors[7, 8] and events[9, 10] occur at younger ages and lower body mass indices (BMI) when compared to other ethnic groups,[10-23] and are rapidly increasing with socioeconomic and nutrition transitions.[4, 24-26] The South Asia region includes three of the top ten countries in the world in terms of total diabetes subjects (India, Pakistan, and Bangladesh)[27] and is the region with the highest number of diabetes-related deaths currently.[28] However deaths are only tip of the iceberg, beneath which are a large number of diabetes patients with complication and long term sequel. A study by Bajaj et al. in 1997 estimated the prevalence of diabetic retinopathy in India to be 20.8%[29], Mohan et al. in 1995 estimated that about 1.9% of the diabetic patients in India develop Nephropathy[29], 23.9% Indians develop diabetic neuropathy (Ramachandran et al., 1988)[29], about 18.5% go on to develop CHD (Mohan et al., 1995)[29], about 3.9% develop peripheral vascular diseases resulting in amputation of 0.5% of these diabetic patients (Mohan et al., 1995).[29] Asian Indians, as a group, are projected to account for between 40-60% of the global CVD burden within the next 10-15 years.[30] Furthermore, 35% of CVD-related deaths in India occur in those between 35-64 years of age as compared to only 12% in the U.S.[31]

Previously it was thought that CMDs were confined to affluent urban residents, but this paradigm is gradually shifting as these conditions are now increasingly prevalent in lower socioeconomic groups in South Asia,[32-34] and CVD is currently the leading cause of death in both urban *and* rural India.[26, 35] Projections suggest that India and Pakistan's national income losses over the decade up to 2015 will amount to US$ 267 billion due to cardiovascular and diabetes deaths alone;[36] of these, the economically active age range (25-64) will bear great morbidity and mortality resulting in loss of human capital and productivity, perpetuating poverty faced by many, and potentially stifling development.

I.iii. Surveillance for the prevalence of CMD and their risk factors

Surveillance of risk factors and disease is an invaluable public health research tool for: monitoring population health status; guiding resource allocation and policy; identifying and prioritizing interventions for subpopulations at particular risk; identifying disparities in outcomes; planning and evaluation of health programs.[37,38] Given the elevated and growing cardio-metabolic risk in South Asia, [7, 10, 13, 19, 23, 25, 26, 39-42] the importance of surveillance cannot be underestimated. Current assessments of surveillance efforts in the subcontinent, and indeed most developing countries,[43, 44] suggest large data deficits, vast state-wise heterogeneity and variable data quality, limiting the value of existing figures.

I.iv. Existing Surveillance system and Gaps

Currently the major source of population level estimates of CMD risk factors, morbidity and mortality in India and Pakistan has been ad hoc surveys. These surveys can generally be characterized as state-specific, with small, often highly variable sample sizes, varying and often low response rates, with use of different diagnostic criteria, and limited by problems of sample design, lack of standardization, frequent measurement errors and incomplete reporting of results.[45] Recent initiatives by the Government of India have attempted to address these deficiencies through setting up a National Program for Prevention and Control of Diabetes, CVD and Stroke (NPDCS), an Integrated Diseases Surveillance Project (IDSP) at multiple sites, and establishing two other NCD risk factor surveillance projects.[46, 47] However, these systems fall short by failing to provide critical CMD-specific incidence and mortality data, measures of diet and physical activity, secular trends in risk factors, health service utilization, health care costs, and quality of care. The Sample Registration System of India, for example, relies on medically certified deaths which account for just 15% of total mortality and coverage is limited to institutional deaths in urban areas.[48] Pakistan conducted a national health survey from 1990-94, but has not mobilized unified, national efforts to collect subsequent health data in keeping with the transitioning socio-political milieu. The region as a whole suffers from a fragmented, chaotic, public-private mix of health-care providers with little or non-existent documentation.

I.v. Arguments for Surveillance Models

Justification for establishment of a well-designed, integrated surveillance system lies not only in helping align resource allocation with actual needs, but also broader themes[49, 50] which include:

a. -More extensive comprehension of the distribution and trends of determinants and disease outcomes, especially given the asymptomatic prolonged course of NCD risk factors, the risk of debilitating target organ damage and often fatal disease events, as well as ensuing health and socioeconomic burdens. This is accomplished by:

   1. -Investigating the determinants of disease prevention through early risk factor detection and control, spanning the spectrum of awareness, knowledge, attitudes, and practice (lifestyle behaviors, health-seeking and utilization, as well as treatment adherence, and perceived quality of life);

   2. -Capturing newly-diagnosed cases, events, recurrent disease and mortality as well as the distribution and determinants associated;

b. -Dynamic integration of information from multiple sources, improving case detection,[51] quality of individual chronic care delivery, health information infrastructure and the opportunity to increase accountability through regular audits and evaluating efficacy of prevention and control strategies;[52-55]

c. -Reducing long-term health expenditure through culmination of safe, effective prevention and care models lowering rates of target organ damage, first events, recurrent disease, disability and premature mortality.

Experiences with surveillance models in developed countries have varied according to the stage of health system maturity and economic development. The U.S., for example, has relied on nationally-representative surveys, focusing primarily on self-reported disease risk factors (National Health Interview Survey, Behavioral Risk Factor Surveillance System or BRFSS). In following trends in cardiovascular risk factors, only one survey (National Health And Nutrition Examination Surveys) now routinely collects laboratory samples.[49] Countries with socialized national health systems, like the UK and Canada, have publicly-funded, networked, routine data capturing registers, although use and auditing of these systems is inconsistent. Models in Australia and much of Europe are based on regular standardized quality of care evaluation, acquiring population characteristics as well as provision of performance indicators based on provider processes and patient outcomes.[49]

The lessons drawn from these experiences and the published literature[49, 50, 49] support the utilization of standardized models that are not reliant on self-reporting, such as the World Health Organization (WHO) STEPwise Approach to Surveillance.[50] An initial, uniform prototype of this nature can be used to overcome infrastructural deficits in low-resource settings, and the foundation created may help advocate for modernizing and scaling up surveillance efforts towards an ideal system (networked,

electronic health recording registers with data integrated from primary care, hospital, laboratory and home monitoring settings).[51, 56]

I.vi. Study partners and their strengths

The Investigators of our study are Drs. **Dorairaj Prabhakaran** (Principal Investigator, PHFI), **K.M. Venkat Narayan** (Emory), **Viswanathan Mohan** (MDRF), **Masood Kadir** (AKU), **Nikhil Tandon** (AIIMS), **K Srinath Reddy** (PHFI) and **Mohammed K. Ali** (Emory). The investigators will work in collaboration with experts in South Asia (Drs. M.V. Padma Srivastava and Sanjay Agarwal in neurology and nephrology, respectively; Dr. Lakshmy Ramakrishnan for cardiac biochemistry; Professors Rahat Mukerjee and R.M Pandey for biostatistics; Dr. Krishna D. Rao for health systems, health economics and program evaluation; Dr. N.K. Arora in clinical epidemiology; Dr. Dwaipayan Bharadwaj in genetics of metabolic diseases and obesity; and Prof. K. Anand in community medicine).

The primary investigators will also have access to CDC consultants (Dr. Ed Gregg for diabetes surveillance and translation; Dr. Ping Zhang for health economics; Dr. Darwin Labarthe for CVD surveillance) and experts from Emory (Dr. Robert Stephenson for quantitative analysis; Dr. Solveig Cunningham for sociology and demography; Dr. Lawrence Phillips for health services research; Drs. Peter Wilson and Abhinav Goyal for CVD epidemiology; Mike Lynn for biostatistics and multi-site study coordination; and Dr. Monique Hennink for qualitative analysis) intermittently, as required. These experts and consultants will not have contact with human subjects or directly influence study design.

The study will be coordinated by a center based at the Public Health Foundation of India (PHFI), New Delhi, India, and by Emory University of Atlanta, U.S.A., as the developed country partner. This center of excellence has been named the Center for Cardiometabolic Risk Reduction in South Asia (CARRS) and will include other partners: Aga Khan University (AKU), Karachi, Pakistan; All India Institute of Medical Sciences (AIIMS), New Delhi, India; and Madras Diabetes Research Foundation (MDRF), Chennai, India. Additionally, the National Center for Chronic Diseases (NCCD) of the U.S. Centers for Disease Control and Prevention (CDC) will be a strategic partner with Emory University, providing technical assistance where necessary.

Our chosen network of partners are intimately familiar with the complexities of the region and appreciate the opportunity and need for context-specific, uniform and sustainable methods of capturing representative estimates of risk factor prevalence and outcomes**.** In addition, through scientific leadership, we aim to implement systems with capabilities for auditing and deriving cost indices, in order to model projected burdens and deliver comprehensive, effective response strategies.[57]

I.vii. Broad Aims of the study

a. - To develop a model surveillance system for CMD and its risk factors which can be adopted - for continuing surveillance by other countries in South-East Asia -

b. - To measure the incidence of CMD risk factors and disease events, as well as the associated - morbidity and mortality -

I.viii. Objectives of the study

Primary objectives

a. - To implement and evaluate a model surveillance system in three study sites namely; Delhi - (India), Chennai (India) and Karachi (Pakistan) -

b. - To assess the prevalence of CMD risk factors and diseases among adults aged 20 years and - above, permanently residing in well-defined urban communities in the three study sites -

c. - Ascertain factors that influence knowledge, attitudes, and perceptions (KAP) of the sample - population regarding CMD and their risk factors -

Secondary objective

a. - Determine the incidence of intermediate risk factors (in previously risk-free individuals), - new-onset complications, and the associated morbidity and mortality -

b. - To derive cost and health-utilization indices which can be used to model projected burdens - of CMD in order to formulate cost-effective and timely interventions -

II. Methodology

II.i. Study design

While the primary study design for the surveillance model is cross-sectional, a cohort study design will be used to follow-up the participants for ~~three~~ four years subsequent to the cross-sectional study. The cross-sectional study will assess the prevalence of CMDs and their risk factors while the pilot cohort study will estimate the incidence of morbidity and mortality associated with CMDs.

The **Cross-sectional study** will be the initial study conducted in 2010-2011 which will also form the baseline for the cohort study conducted in subsequent years. A repeat cross-sectional survey will be conducted in ~~2013-2014~~2014 by recruiting an independent sample in the same study sites to estimate the trend (over 4 years) in prevalence of CMDs and their risk factors.

The **Cohort study** will follow the cross-sectional ~~study~~ studies and will be conducted between 2011 and ~~2014~~2015. With informed consent, subjects enrolled into the 1st cross-sectional study will be

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followed up as a cohort for ~~three~~ four years and the 2nd cross-sectional study will be followed up ~~for~~after one year to measure the outcomes of interest.

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Outcomes of interest:

i. Anthropometric Changes
   a. Weight
   b. Waist Circumference
   c. Skinfold Thickness
   d. Body Fat
ii. Development of new-onset intermediate risk factors
   a. Hypertension
   b. DM
   c. Dyslipidemia
iii. Incident morbidity
   a. Stroke
   b. MI
   c. CHF
   d. Chronic Stable Angina
   e. Chronic Kidney Disease
iv. Complication
   a. PVD
   b. Retinopathy
   c. Nephropathy
   d. Neuropathy
   e. Amputation
v. Health service utilization and costs
   a. Hospitalization
   b. Outpatient use
vi. Mortality
   a. All cause
   b. CMD-specific

II.ii. Study sites and settings

The Surveillance study will be conducted in three sites, two in India (Chennai and New Delhi) and one in Pakistan (Karachi). This will be a household survey wherein recruitment of participants and data collection will take place in the households. These are metropolitan urban settings with large, growing populations (an estimated 4.5, 10 and 13.8 million people live in Chennai, Karachi, and New Delhi respectively) and represent archetypes of rapid socio-economic, demographic, epidemiologic, and nutrition/lifestyle transitions. These cities are characteristic of the endogenous regions in which

they are situated and are home to both urban and semi-urban populations of varying socioeconomic status.

II.iii. Sample size estimation

We have applied the WHO STEPwise methodology [59] to estimate the sample size required to capture CMD risk factor prevalence precisely across the three study sites in South Asia. Utilizing risk factor prevalence estimates from previously published Indian studies and anticipating a response rate of 80 per cent (%) with a design effect factor of 1.5 (to account for cluster sampling), the sample size estimates were generated for males and females in three age strata (20-45, 45-60, 60 and above) in each urban setting. Table-1 presents the cumulative subtotals of subjects required to observe appreciably consistent prevalence approximations for each of the commonly-known risk factors. As shown, the highest required sample size (3,983 people) will permit each site to reliably estimate one or more of the CVD risk factors for each of the gender and age strata identified above.

Beyond this, we will conduct follow-up surveys to collect pilot data on incidence of risk factors, CMDs complications, and CMD-specific mortality. Consent will be taken during the initial recruitment for the cross-sectional survey and only those participants who provide consent to be followed up for three years will be enrolled into the study. However we anticipate an overall 15% loss-to-follow-up by the end of the cohort study especially due to high probability of migration of the young population (20-35 years) due to job opportunities or marriage (in case of females), and also because the study is community based.

Table 1: Sample size estimation (per site)

Risk factors	Level of Confidence	Margin of Error	Baseline levels of indicators	Design effect	Expected Response Rate	No. of age/sex Estimates	Sample size
Tobacco use	1.96	0.05	0.23	1.5	0.8	6	3062
Hypertension	1.96	0.05	0.36	1.5	0.8	6	**3983**
Diabetes	1.96	0.05	0.15	1.5	0.8	6	2204
Overweight (BMI ≥ 23)	1.96	0.05	0.65	1.5	0.8	6	3933

II.iv. Sampling methodology

A multi-stage cluster random sampling technique will be used to capture a sample representative of the urban population at the three sites. Each of the cities has its own distinctive municipal sub-divisions, encompassing municipal corporations, wards and census enumeration blocks (CEB) from which households will be randomly selected. After the households are selected, a three step within-

household sampling methodology based on the method used in the 2002 Health Information National Trends Study (HINTS) conducted in the US[58] will be used to recruit the study participants. With informed consent, two subjects will be selected per household, one male and one female aged more than 20 years. However it is anticipated that in some households only one eligible participant may be found. The final sample for the cross-sectional survey will be composed of equal proportions of males and females in each of the three age strata (20-45 years, 45-60 years and >60 years) leading to a sample of 4000 participants in each of the study sites (fig-1, fig-2 & fig-3). To achieve 4000 participants with all the parameters measured (blood biochemistry, anthropometry, bioimpedence and blood pressure) we will need to recruit 5500 participants at each site (with 75% response rate for blood sample. Due to budgetary constraints, Karachi site will stop at 4000 sample size, Delhi and Chennai will continue to recruit 5500 participants at each site. In year 2014, an independent sample of 6,500~~,~~ participants in each of the three cities (~~15,000~~19,500 total) will be recruited ~~in all three cities~~ for the 2nd cross sectional survey.

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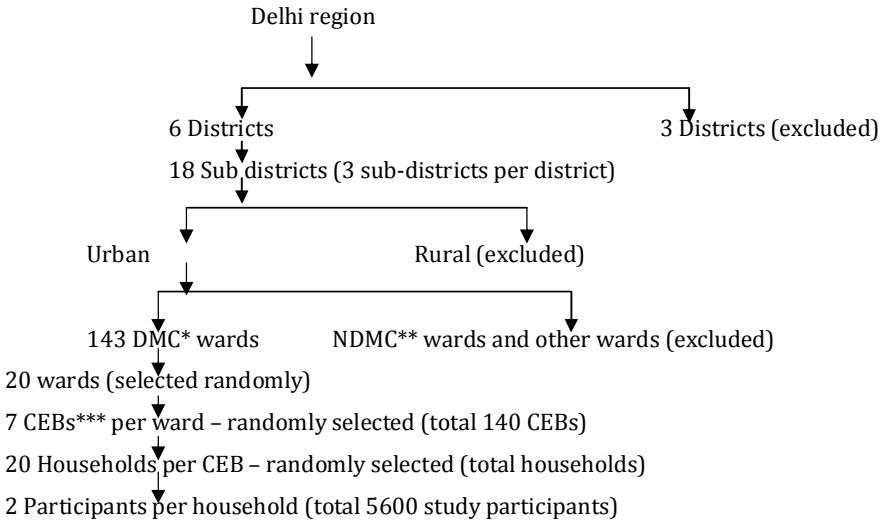
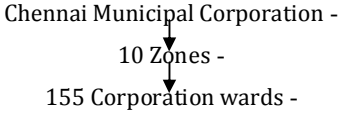
Diagrammatic representation of city subdivisions for sampling

Figure 1: New Delhi Sampling Scheme



*Delhi Municipal Corporation; **New-Delhi Municipal Corporation, ***Census Enumeration Blocks

Figure 2: Chennai Sampling Scheme



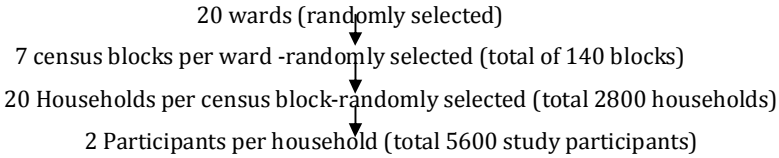
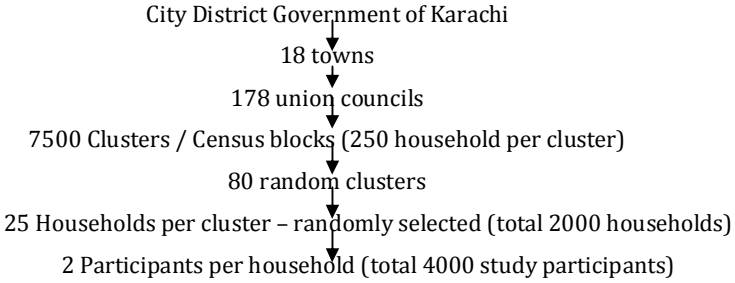


Figure 3: Karachi Sampling Scheme



II.v. Study tools

Standardized sampling will enhance representativeness and reproducibility of results. Utilizing uniform tools and methods is a key component of this process and more easily replicable across multiple sites. We will consult validated questionnaires from the WHO Multinational MONItoring of trends and determinants in CArdiovascular disease (MONICA) study, WHO STEPwise Surveillance methodology, and existing questionnaires from regional and national surveys (accessible via partners at CDC), to construct a culturally appropriate and methodologically relevant questionnaire for South Asia. Validated and new event (CVD or target organ damage) capturing tools will be adapted to verify questionnaire-based follow-up survey incidence findings.

II.vi Surveillance indicators

A baseline cross-sectional survey of 15,000 participants (n=5,500 at Delhi and Chennai and n=4000 at Karachi) in 2010-2011 and a second baseline cross-sectional survey of ~~15,000~~19,500 participants (n=~~5,000~~6,500 at Delhi, Chennai and Karachi will gather information encompassing broad categories such as: demographic and socio-economic characteristics of the population; presence of risk factors; previous or existing target organ damage (known nephropathy, angina, retinopathy, cataracts, peripheral vascular disease, previous stroke, previous therapeutic procedures such as amputation, revascularization procedure, peripheral endovascular procedure, dialysis, transplant, laser photocoagulation); quality of life, disability, health care utilization; quality, and cost(s) of care (as described in table-2). Surveys will be comprehensive and encompass collection of data, anthropometric measures, venous blood samples, urine samples and saliva.

Demographic and social characteristics of the population will be collected including information regarding age, sex, marital status, religion, education, income, occupation, migration and household assets. Apart from this meticulous collection of contact details of participants will help in following up the cohort and minimize loss to follow up. Validated questionnaires will be used to collect this information.

Several components of female reproductive history have been found to be associated with CMD and their risk factors. A detailed history on menarche, gestation, menopause and contraception will be taken through validated questionnaires to find any such association in our study population.

This study will assess both the distal and intermediate risk factors for CMD. Distal risk factors of interest are mostly related to lifestyle and include alcohol use, dietary habits, physical activity, stress and tobacco use. The intermediate risk factors will include study of prevalence of hypertension, obesity, diabetes and dyslipidemia. Tools that will be used to measure distal risk factors are validated questionnaires (food frequency questionnaire, physical activity questionnaire, etc.) and laboratory tests to confirm tobacco use in 15% of randomly selected participants through measurement of Cotinine in saliva. The intermediate risk factors will be assessed through anthropometric measurements (Height / Weight / Waist Circumference/ Skinfold thickness / Body Fat), blood pressure measurement and through tests of bio-chemical parameters (laboratory estimation of FPG, HbA1c, Lipid profile, ApoA/B, serum urea and creatinine)

Prevalence of certain morbidity indicators of CMD will be studied. These include disability from Stroke, MI, CHF, Amputation, Chronic Stable Angina, CKD, revascularization, and other procedures and hospitalization related to CMD. This will be assessed through validated questionnaires and cross-checked with medical records.

Table 2: Summary of the Surveillance Indicators

Indicators	Measures	Methods
Demographic and Social Characteristics	Age / Sex / Marital Status / Religion	Questionnaires
	Education / Income / Occupation	
	Household assets	
	Contact Details (and supplemental contacts)	
Female Reproductive history	Menarche/ Gestational history (PIH, GD), Menopause (surgical / physiological / whether on HRT) / Contraception	Questionnaires
Distal risk factors	Alcohol Use / Dietary Habits / Physical Activity / Stress	Questionnaire
	Tobacco use	Questionnaire / Cotinine in saliva
Intermediate risk factors	Hypertension	Clinical Examination, BP measurement
	Dyslipidemia	Laboratory estimation of serum TC, LDL, VLDL, HDL, Triglycerides, ApoA/B
	Obesity	Anthropometry (Height / Weight / Waist Circumference / Skinfold thickness / Body Fat)

Indicators	Measures	Methods
	Diabetes	Laboratory estimation of FPG, HbA_1c
Morbidity	Stroke / MI / CHF / Chronic Stable Angina	Questionnaires including medication history; Medical records of documented events or procedures, serum urea and creatinine and albumin for CKD
	CKD/ Dialysis / Renal transplantation	
	Amputation/diabetic retinopathy	
	Procedures, Revascularization, Hospitalization	
Quality of Life -	Mobility, self care, usual activities, pain/discomfort, anxiety/depression (related to CMD and their risk factors)	EQ-5D
Health services, Quality of Care and Health care costs	Awareness and Risk Factor Control	One-to-one Interview, Questionnaire,
	Access to Health Care Services	One-to-one Interview, Questionnaire
	Utilization of Services	One-to-one Interview, Questionnaire
	Health Insurance / Coverage	One-to-one Interview, Questionnaire
	Costs of Treating CMDs and CMR	One-to-one Interview, Questionnaire
Genetic and metabolomic studies	To identify genetic determinants of CMDs and their risk factors	Genome-wide association studies (GWAS)

BP = blood pressure; FPG = fasting plasma glucose; HbA_1c = glycated hemoglobin; TC = total cholesterol; HDL = high-density lipoprotein cholesterol; LDL = Low density lipoprotein; VLDL = Very low density lipoprotein; ApoA/B = apolipoproteins A & B; BMI = body mass index; MI = myocardial infarction; CHF = congestive heart failure; CKD = chronic kidney disease; CMD = cardio-metabolic disease; EQ-5D = European Quality of Life 5 Dimensions questionnaire.

II.vii. Study of cost burden

The study will utilize a **bottom-up**, **cost-of-illness approach** to collect important data on: -

- ***health-service utilization and treatment patterns*** (assessing the patterns of health-seeking, and treatment regimens that are used widely)
- ***direct costs*** ('inputs' encompassing out-patient and in-patient care, pharmacotherapies, therapeutic procedures, and transportation to and from health care facilities in a given timeframe);
- ***indirect costs*** ('lost outputs' representing the value of economic productivity lost by society on account of temporary or permanent absence, disability, or premature mortality);
- ***health-related quality of life*** (including health utilities); and
- ***health outcomes*** (including incidence of new-onset risk factors, CVD events, morbidity, and mortality),

that may be used to model **societal burdens** of disease and potential avoidable mortality, disability, and costs with addition of proven interventions. Direct medical and non-medical costs will be ascertained from respondents through standardized questionnaires applied in other low- and middle-income countries. Data will also be collected from providers in different settings (private and

government-funded clinics) to provide corroborated data for sensitivity analyses. Indirect costs will be estimated using a human capital approach which is based on data regarding absence from work and unit costs derived from national wage rates (for different occupation classes).

Lost production = total absence X wage rate of workers

Where possible, data regarding caregiver time and costs will be ascertained and included in analyses. The study will not collect data regarding foregone opportunities of children or other household members.

II.viii. Qualitative exploration

II.viii.a. Background

There is very little currently published regarding the knowledge, perceptions, attitudes, and care practices of people with cardio-metabolic risk factors and diseases in South Asia. The surveillance study serves as a robust platform for investigating these qualitative aspects of cardio-metabolic diseases.

II.viii.b. Study questions

1. - Identify valid indicators for assessment of the economic burden of CMD and their risk factors in different socioeconomic backgrounds and regions.
2. - Analyse the temporal trends and peculiarities of the socio-economic effectsKnowledge, attitudes, perceptions, and practices of persons with risk factors (DM, HTN, Dyslipidemias, Smokers)
3. - Knowledge, attitudes, perceptions, and practices of persons with cardiovascular (chronic stable angina, previous MI or UA, previous revascularization, PVD, previous stroke) and chronic kidney diseases
4. - Factors that influence self-care and health-seeking in South Asia amongst those with risk factors and vascular diseases
    i. - Continuity of care
    ii. - Normal versus alternative forms of health care
    iii. - Trends and peculiarities associated with self-care and health-seeking in this region of the world
5. - The patient's experience with and without existence of complications (cardiac, eye, renal, foot, and neurological illnesses that result from diabetes and hypertension)

II.viii.c. Methodology

- Careful selection of cases

- Cases will be participants who are known patients of any of the CMDs with or without complications
- Sampling methodology - purposeful sampling (grounded theory) - 10-25 cases per site, each subsequent case will be decided based on the interview and analysis of the existing samples
- One-to- one interview
- Identification of issues through preliminary interviews which will determine the direction and the necessity of further interviews and selection of cases

II.ix. Study outcomes

We will conduct follow-up surveys to detect anthropometric changes, incidence of new intermediate risk factors or changes in participants with pre-existing risk factors (either or multiple of hypertension, diabetes, and dyslipidemia), morbidity (underlying target organ damage, health consequences, and disability) and mortality associated with CMDs during the follow-up study of the cohort for three subsequent years. CMDs and their complications will be diagnosed using standard definitions (described in the MOP) and will be coded using MedDRA / ICD codes. The outcomes of interest are described in section II.i.

Table 3: Outcome Indicators in Follow-up Surveys

Outcome	Measures	Methods
Anthropometric Changes	Height / Weight / Waist Circumference / Skinfold Thickness / Body Fat	Clinical Examination, Stadiometer, Weighing Machine, Tape Measure, Calipers, Bio-electrical impedance
Intermediate risk factors (during the third follow-up only)	Hypertension	Clinical Examination, BP measurement
	Diabetes	Laboratory estimation of FPG, HbA_1c
	Dyslipidemia	Laboratory estimation of serum TC, HDL, Triglycerides, ApoA/B
Incident Morbidity	Stroke / MI / CHF / Chronic Stable Angina	Follow-up surveys; Medical records of documented events, admissions or procedures; Rose Angina Questionnaire, serum urea and creatinine for CKD.
	CKD/ Dialysis / Renal transplantation	
	Amputation/diabetic retinopathy/ Procedures /Revascularization/ Hospitalization	
Mortality	All cause	Follow-up surveys; Death Certificates; Verbal Autopsy (WHO)
	CVD-specific; Diabetes-specific	

BP = blood pressure; FPG = fasting plasma glucose; HbA_1c = glycated hemoglobin; TC = total cholesterol; HDL = high-density lipoprotein cholesterol; LDL = Low density lipoprotein; VLDL = Very low density lipoprotein; ApoA/B = apolipoproteins A & B; BMI = body mass index; MI = myocardial infarction; CHF = congestive heart failure; CKD = chronic kidney disease; CMD = cardio-metabolic disease; EQ-5D = European Quality of Life 5 Dimensions questionnaire.

II.ix. Biological sample collection and storage

Biological samples to be collected include 15 ml of blood, 100 ml of urine and 10 ml of saliva. Depending on the study site's experience with previous community based studies, blood samples (fasting), urine sample (first morning void) and the sample of saliva (fasting) will be collected at the participant's residence or by organizing camps/clinics. These will be transported in proper cold chain to the laboratories at the field site, where the analysis will be done (described in table-2 and 3). The sample will then be stored in cryo-vials for future analysis. The challenges of collection, handling, transfer, and storage of specimen samples can be offset by many of the quality assurance plans. Maintaining the condition of samples from collection to long-term storage facilities is crucial to surveillance research, so we will integrate procedures and policies that ensure clear labeling, temperature control, pre-emptive solutions to power failure and safety for all field staff from biological hazards. The methods of analysis of the biological samples at each of the three study sites are given in table-4.

Table 4: Biological samples and their methods of analysis

Clinical parameter	Laboratory parameter	Methods used for analysis		
		Chennai	Delhi	Karachi
Diabetes	Fasting plasma glucose	Hexokinase/Kinetic*	Same as that of Chennai	Oxygen rate method
	HbA1c	HPLC*		HPLC
Dyslipidemia	Total cholesterol	CHOD-POD/End point*		Enzymatic Colorimetric method
	HDL	Direct*		Enzymatic Colorimetric method
	LDL	Friedwald Formula		Enzymatic Colorimetric method
	VLDL	Calculation		Calculation
	Triglycerides	GPO-PAP/End point*		Enzymatic Colorimetric method
	Apo A, Apo B	Immuno-turbidimetric*		**Not done**
Kidney disease	Serum urea	Urease GLDH/ Kinetic*		BUN: Enzymatic conductivity rate method
	Serum creatinine	Jaffe Kinetic*		Modified Jaffe's Method
	Microalbuminuria	Immuno-turbidimetric*		Rate nephelometry
Tobacco	Salivary cotinine	Not done		Not done

exposure				

*Auto-analyzer

III. Data management

III.i. Data collection

Data will be collected through paper based, interviewer administered questionnaires in the participant's house. For the cross-sectional survey this will be accomplished through two visits. Thereafter one follow-up visit for each participant will be done at an interval of one calendar year. The implementation process of the study tools are described in table-5. The interviewers will be rigorously to minimise errors and constantly supervised. Quality assurance will be through monitoring and evaluation discussed in section VI.

Table 5: Implementation of study tools

Year	Schedule	Household proforma	Demographic and residential details	Tobacco, alcohol, diet, physical activity and stress	Female reproductive health	Medical history	Co-morbidities	Complications	EQ-5D	Respiratory disease	Family history	Treatment history and expenditure	Anthro-pometry/BP	Blood	Saliva	Urine	Verbal Autopsy/ Death Certificates
Cross Sectional Study-I																	
2010-2012	Participant recruitment	X															
	Data collection		X	X	X	X	X	X	X	X	X	X	X	X	X	X	
***~~Cohort~~ Cohort -1*(Follow-up)**																	
2011-2012	Follow-up - 1			X		X	X	X	X			X	X				X
~~2012-2013~~2013	Follow-up - 2			X		X	X	X	X			X	X	x		x	X
~~2013-~~2014	Follow-up - 3			X		X	X	X	X			X	X	~~X~~		~~X~~	X
2015	Follow-up-4			X		x	x	x	x			x	x	x		x	x
Cross Sectional Study-II																	
~~2013-2014~~2014	Participant recruitment	X															
	Data collection		X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Cohort -2 (Follow-up)																	

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2015	Follow up			X		X	X	X	X			X	X				x

EQ-5D: European Quality of life five dimensions Questionnaire

III.ii. Data entry

An online database will be created using Microsoft access having a user friendly data entry screen in English. A data field specification list will be created along with a coding list for designing the database. The database will be programmed to have automated in-built checks for, logic, clinical reasonable such as ranges, absolute and relative values, context and structure. This will control the quality of data. The database will be assessed during the pilot study and necessary restructuring done before finalising it.

Data will be entered in the entry forms of the database at the respective study sites (MRDF, PHFI & AKU). Double data entry will be done for 25% of the forms to cross-check errors. There will be regular checks by site coordinator to minimise errors, missing values and outliers. Any errors found will be corrected by referring to the filled questionnaire or if required by a revisit to the participant. Data entry completion and errors will be continuously monitored at COE-CARRS. All queries (site/participant/ field/ interviewer) raised by COE-CARRS will have to be resolved by the field site at the earliest. Final data cleaning and de-linking of participant identification information will be done at PHFI before conducting the analyses. (Details are provided in Section VI.i.2 and VI.i.3)

III.iii. Data analysis

(a) Quantitative Analysis

Data analysis will be staggered to correspond to follow completion of each survey. All statistical analysis of quantitative data will be done using Statistical Analysis Software (SAS, version 9.1, SAS Institute, Cary, N.C)[60] or STATA (Statacorp, TX).[61]A probability of $p<0.05$ will be considered statistically significant for all tests. Assumptions of normally-distributed data will be assessed using plots and tests of normality. Non-normal variables will be transformed or categorized as required. All data will be presented before and after adjustment for confounding and testing for interactions.

Descriptive data analyses will be performed for all variables. Means, standard deviations, quartiles, and median levels of risk factors for each gender and age group will be reported. Comparisons across gender, age groups, sites, and time periods will also be done using Chi-square and logistic regression for categorical variables, and t-tests and linear regressions for continuous variables. Evaluation of predictors of incidence and mortality will employ Cox's proportional hazards models. Response rates and percent retention will be evaluated by comparing the number of eligible individuals approached, number agreeing to participate, and successful follow-up over duration of surveillance studies.

(b) Qualitative Data Analysis

All interviews will be de-identified prior to analysis. The MAXqda (2007) program will be used to manipulate textual data for analysis. Analysis of the textual data will follow the grounded theory methodology whereby key themes are identified inductively from the textual data. These themes will then be compared using structured comparisons to identify specific issues.

IV. Reporting and publication

At defined points over the course of the four years, formal analysis of quantitative and qualitative data will be reviewed for validity and subsequent publication. The investigators have formed a Publication, Presentation, and Patents subcommittee led by Drs. K.M. Venkat Narayan and K. Srinath Reddy, and they are currently developing a suitable policy to protect the COE's rights regarding ownership of study materials and data. The investigators will be the custodians responsible for assigning subgroup analyses and publication under the oversight of this subcommittee. Reported outcomes of interest will include: age-standardized prevalence and mean levels of CMD risk factors; incidence rates for emergence of risk factors, disease events, and mortality; levels of awareness; health care costs; health service utilization; quality of life and determinants of human behaviors (qualitative measures).

V. Quality assurance

V.i. Quality assurance strategies

Quality assurance strategies will be applied throughout the duration of the study using a framework which comprehensively considers each phase of the study and applies inter-related themes to every level of the study (as shown in table-6).

Table 6: Quality assurance strategies

		Phase			
		Design and Planning	**Pilot Testing**	**Data Collection**	**Data Analysis**
Levels	**COE -CARRS**	• Critical review of protocols (IRB)* • Develop a common manual of operations • Coordination of timelines, activities	• Assess fluidity and feasibility of field operations	• Monitoring field activities	• Audit and evaluate validity of findings prior to publication • Internal peer reviews prior to publication
	Investigators	• Certification • Pre-situational analysis	• Audit results after pilot is completed	• Monitoring	• Validity checks • Review results
	Field Personnel	• Extensive training • Objective evaluation • Easy-to-carry SOPs **	• Evaluate all field and documenting techniques	• Random checks, re-training	
	Survey Questionnaires	• Peer-review • Translation into local language(s) • Internal consistency estimates and reliability exercises	• Establish clarity and face validity in small field sample	• Regular checks to assess completeness	• Identify and discard compromised or inadequately com-pleted questionnaires
	Measuring Equipment	• Central procurement • Central training • Calibration guidelines and checks	• Evaluate calibration techniques, acceptability of use in field	• Regular calibration of tools; replace as and when required	
	Specimens	• Central procurement of kits and equipment • Specific protocols for each biochemical assay • Training (labelling,	• Evaluate adherence to protocols, labelling, processing,	• Random checks • External temperature gauge labels to monitor sample	• Stored samples for future investigation • Identify and discard compromised

	Phase			
	Design and Planning	**Pilot Testing**	**Data Collection**	**Data Analysis**
	handling, storage)	storage and handling • Interim analysis to detect outliers	temperature	samples
Laboratory	• Laboratory selection and identification of reference laboratory • NABL or CAP certification *** • Central procurement before distribution • Develop internal and external quality assessment protocols and schedule of regularity	• Evaluate procedural fluidity • Evaluate intra- and inter-laboratory variability • Interim analysis to detect outliers	• Internal quality checks and calibration • Regular external validation – lyophilized samples from reference laboratory	• Assess intra- and inter-laboratory coefficients of variation
Communication	• Establish reporting structures • Establish data transfer plans	• Assess agility of transfers		
Documentation	• Develop checklists, logbooks • Training in appropriate and legible documentation	• Assess recording legibility		• Audit logbooks for response rates and field activity indicators
Data Storage & Confidentiality	• Establish data back-up and protection policies • Training of all staff	• Assess accessibility, simplicity and flexibility of software	• Locked and password-protected data storage • Active back-up	• De-identified datasets • Limited access to personal identifiers
Data Entry	• Establish protocols, consistent data cleaning methods and verification systems	• Assess variability	• Interim analyses to identify duplicate entries • Decision log to document issues	• Reporting on outliers • Validity checks • Track database errors

**IRB = institutional review board; **SOP = standard operating procedures; ***NABL = National Accreditation Board for Testing and Calibration Laboratories, Department of Science and Technology, Government of India; CAP = College of American Pathologists, Northfield, IL, USA*

Validated questionnaires will be used to design the survey questionnaire and these along with the data collection forms will be peer-reviewed to ensure construct validity. Further the questionnaire will be pilot-tested in a small sample of population to ensure face validity. Details of quality assurance for instruments are mentioned in sectionVI.i.2. Rigorous training and familiarity with tools will minimize intra- and inter-observer variability. Key considerations throughout the process are consistency, strong leadership, communication, and adherence to clearly defined roles.

V.ii. Anticipated challenges in quality assurance and suggested solutions

(a) Representativeness of Sample

Given the heterogeneity in socioeconomic status, cultural, nutritional, and linguistic characteristics of the sample populations derived from distinct sites, the investigators anticipate challenges in capturing samples that are representative of the wider South Asia region, and that inherent differences may limit generalizations in deductions made. A detailed sampling frame with

meticulous application should prevent concerns of representativeness, while stratified analyses may elicit consistent differences in population characteristics.

(b) Response Rates and Loss to follow-up

Further concerns include encountering low response rates as well as loss to follow-up of participants. Suggested solutions are: (a) engaging communities to be sampled in advance and obtaining approval from local authorities; (b) leveraging our institutional reputations; (c) methodical application of training, regular surveyor motivation and encouraging positive, professional and respectful behavior towards respondents; (d) advance scheduling of visits that are convenient for respondents, and providing a list of subsequent visits; (e) storing and backing up contact details of all respondents surveyed and supplemental contact information (for relatives, employers) in an accessible format, while appealing to those surveyed to notify the network surveillance site office of any change of contact; and (f) identifying those at risk of mobility and customizing our approach accordingly. Our investigators have extensive experience in recruiting and maintaining population cohorts (e.g., Industrial Health Study, New Delhi Birth Cohort Study, CUPS, and CURES).

VI. Monitoring and evaluation

A Quality Monitoring and Evaluation (QME) sub-committee will be responsible for quality assurance of the study, will monitor all phases of the study and will conduct formative, process and outcome evaluation. The QME sub-committee will include the principal investigators, senior field personnel, site coordinators and external evaluators. Progress of the study will be monitored through regular appraisal by the QME sub-committee. Each site will be visited by an external evaluator twice in a year. This will help to maintain the timeline of the study.

VI.i. Procedures for evaluating the process of the study

VI.i.1. Sampling*:*

a. - After the list of households is prepared, random checks will be done especially for areas that have been undergoing continuous development to ensure that all households are enlisted.

b. - Cross-check the random household number generated with the number of the household in which participants were interviewed.

VI.i.2. Data collection**:**

a. - Initial shadow monitoring of all interviewers will be done for practical training and to resolve issues immediately. This will also help to identify weak personnel who may require intermittent supervision.

b. - As the study progresses, random checks for about 5-10% of the participants will be done every three months by site coordinators and project managers who will verify some of the answers in the filled questionnaires (visit-1).

c. - Random checks will be done during visit-2 (anthropometric measurements and biological sample collection). There will be regular visits by evaluators to the clinics/camps where anthropometric measurements and biological sample collection is being done. The monitors will check for instrument calibration (as per the calibration protocol for this study-details provided in manual of operations) and also assess the collection, handling and storage of biological specimen. Temperature of specimen storage equipment will be monitored to check the maintenance of log books and temperature charts. Faulty instruments will be replaced and technicians will be re-trained to correct any immediate issue. Any sample whose quality is compromised will be discarded and if possible a second sample will be collected from the participant. However, minimal technical problems are anticipated as all technicians selected will be thoroughly trained.

d. - Laboratory monitoring: Internal quality control checks will be done regularly. About 10% of the samples will be re-analysed at a reference laboratory from each site. Inter-site quality checks will also be done through exchange of 5% of the samples. Inter and intra laboratory coefficient variation will be conducted to standardise results across all the study sites and control bias.

e. - There will be regular documentation of the response rates from participants especially for the follow-up of cohort to minimise loss to follow-up. The QME will also be responsible to audit these rates and other documented field activity indicators such that immediate corrective measure can be taken.

VI.i.3. Data entry:

At site:

a. - Site coordinators will be responsible for checking all forms for completion or for any obvious errors before data entry.

b. - In-built checks in the software – logic checks, context checks and ranges will be incorporated for outliers.

c. - The outcomes of cohort study for all participants will be validated by physicians and intra and inter observer variability will be checked by the site coordinator and / or an external evaluator before data is entered

d. - Expected error rates: Every time an error is located it will be given a mark of one, once all participants' and field data are checked (all fields, all rows, all columns), the error marks will be summed and using denominators of total fields, context fields and outcome fields, error rates for all fields, context fields and outcome will be respectively generated. The error rates

are usually expressed as errors per 10,000 fields[62] [2]. Error rates vary for studies and different studies use different rates as acceptable limits[62, 63] [1, 2]. Since it is a large study with a very large number of data fields, we use the error rates suggested by Neaton et al. [2], 10 errors per 10,000 fields or 0.001. However, for context or participant identification / demographic fields and for outcome fields "zero tolerance" will be used (acceptable error rate=zero) [1, 2].

Error rate – all fields (0.001) -

Error rate – context fields (Zero) -

Error rate – outcome of cohort study (Zero) -

e. - Any errors found will be corrected by referring to the filled questionnaire or if required by a revisit to the participant.

At the COE-CARRS:

a. - The data manager and statisticians will re-check all data sent from the sites for outliers, coding errors and missing values.

b. - The data will be checked for missing values, outliers and inconsistency by running do-files. Queries will be generated for inappropriate data and query rates will be calculated for sites, interviewers and outcome.

c. - Expected query rates: Every time a query is located it will be given a mark of one, once all data are checked for all sites, the query marks will be summed and using denominators of total fields per site, total fields per interviewer per site and total outcome fields per site, query rates for site, interviewer and outcome will be respectively generated. Acceptable query rates will be same as the error rates described above, 0.001 for site and interviewer and zero for outcome fields.

Query rate – Site (0.001) -

Query rate – interviewer (0.001) -

Query rate – outcome for cohort study (zero) -

d. - Apart from this about 10% of randomly selected paper questionnaires will be sent to COE-CARRS from each site at an interval of three months. These will be checked for error and error rates will be calculated as described above.

e. - Measures to be taken if the query and error rates are higher than the pre-decided value:

- High query/error rate for site - all data for the site will be checked against paper forms at the study site.
- High query/error rate for interviewer – all data for the particular interviewer will be checked against paper forms at the study site.

- If there is any error in the outcome for the cohort study, first the data will be cross-checked against paper forms and if required the participant will be re-visited. If none of these can correct the error, the error field will be dropped as missing.

f. - Once re-checking of the data at COE-CARRS is complete it will be freezed and if the site requires any updating, the data will be sent with proper reasoning to COE-CARRS who will review and make the necessary changes.

g. - Decision log will be used to document all issues related errors and queries (using excel sheets and emails)

h. - Monitoring data storage and confidentiality procedures: This will be done by the PIs and external evaluators at the COE-CARRS after the complete collation of data and before using the data for analysis.

VI.ii. Procedures for evaluating the outcome of the study

1. - After the study is complete an independent evaluation will be done by the PIs and the external evaluators to ascertain if the aims and objectives of the study are fulfilled. This will be done through review of all the preceding evaluation processes, and also through review of the findings and results of the study.
2. - The report will be presented to the Steering Committee for final comments.

VII. Ethical considerations

Informed consent for interview, anthropometric measurements and blood collection will be taken from all individuals before enrolling them into the study. The study anticipates no major risk to participants except needle pricks for collection of blood sample during the cross-sectional survey and thereafter during the third follow-up of the participants. There could be rare instances of bleeding from the puncture site, however trained technicians and nurses will minimise even the rarest of such possibility. Needle prick injury to the technicians is also anticipated, however these will be minimised by adopting universal safety precaution. Strict confidentiality of the information provided by the participants will be maintained and all possible source of identification of participants will be delinked before using the data for analysis. The blood samples collected will be solely used for the purpose of this study.

VIII. Study organization

1. - Funding Agency: National Heart, Lung and Blood Institute (NHLBI), National Institutes of Health (NIH), USA and Ovations Chronic Disease Initiative, United Health Group, USA.

2. - Key Coordinating centres: The study will be coordinated by Center for CArdio-metabolic Risk Reduction in South Asia (CARRS) at Public Health Foundation of India (PHFI), New Delhi, India, and by Emory University of Atlanta, U.S.A.

3. - Principal Investigator -

   Dr. Dorairaj Prabhakaran (PHFI, New Delhi) -

4. - Collaborators:

   a) - International

   Centre for Disease Control (CDC) consultants: Dr. Ed Gregg for diabetes surveillance and translation; Dr. Ping Zhang for health economics; Dr. Darwin Labarthe for CVD surveillance.

   Emory consultants: Dr. Robert Stephenson for quantitative analysis; Dr. Solveig Cunningham for sociology and demography; Dr. Lawrence Phillips for health services research; Dr. Peter Wilson and Dr. Abhinav Goyal for CVD epidemiology; Mike Lynn for biostatistics and multi-site study coordination; and Dr. Monique Hennink for qualitative analysis.

   b) National

   Dr. M.V. Padma Srivastava in neurology and Dr. Sanjay Agarwal for nephrology, Dr. Lakshmy Ramakrishnan for cardiac biochemistry; Professors Rajat Mukerjee and R.M Pandey for biostatistics; Dr. Krishna D. Rao for health systems, health economics and program evaluation; Dr. N.K. Arora in clinical epidemiology; Dr. Dwaipayan Bharadwaj in genetics of metabolic diseases and obesity; and Prof. K. Anand in community medicine.

5. - Steering Committee

   a. - Members: Dr Dorairaj Prabhakaran (PHFI, New Delhi), Dr Venkat Narayan (Emory, Atlanta), PI of ACC and NHLBI Staff

   b. - Activities: Regular teleconferences among steering committee members and annual steering committee meetings to the undertake the following activities – Protocol changes, monitoring of recruitment rate, monitoring of follow-up rate for necessary changes

6. - Quality Monitoring and Evaluation (QME) sub-committee:

   a. - Members: Principal investigators, senior field personnel and external evaluators

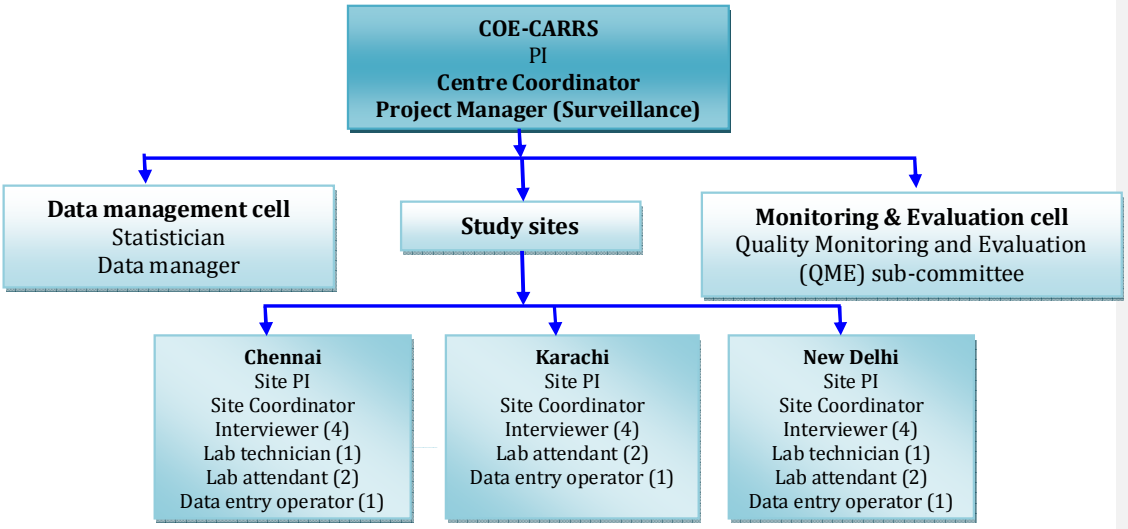
   b. - Activities: Described in section VI.

7. Study Team

Each of the three study sites has a team who is involved in all phases of the study starting from study design to implementation, data collection, data entry, data processing, and monitoring and evaluation of the study to ensure quality control and smooth operation. In addition to this the COE-CARRS at PHFI, New Delhi will coordinate with the three study sites and is the focal point for the study. The final data processing, analysis and reporting will be done at the COE-CARRS.

a. Team members at COE-CARRS (PHFI): Dr Dorairaj Prabhakaran (PI)
b. Team members at Madras Diabetes Research Foundation (MDRF), Chennai: Dr Viswanathan Mohan (PI) and Dr Pradeepa Guha
c. Team members at Aga Khan University, Karachi: Dr.Masood Kadir (PI), Dr. Rehana Siddique

Figure 4: Organogram of study organization



IX. Timeline

The Surveillance Study will be conducted over a period of ~~five~~ six years. The first baseline cross-sectional survey will begin in 2010 with estimated completion time of twelve months. The participants will be then followed up as a cohort with annual follow-up surveys for four ~~three~~ subsequent years. ~~Another~~A baseline cross sectional survey will be conducted on newly recruited participants in 2014 and ~~then~~they will be followed up as a cohort with annual follow-up survey in 2015~~for next year.~~ Data analysis and reporting will take place after the collation of data at the end of the cross-sectional survey and thereafter at the end of annual follow-ups in each study site. Monitoring will be an ongoing process and the system of evaluation will be inbuilt into the study. The details of the timeline are provided in table-7.

Table 7: Timeline for Surveillance Study

Activities	2010	2011	2012	2013	2014	2015
Study initiation activities (field staff recruitment, training and piloting of study)						
Household and participant recruitment						
Random selection of households and recruitment of study participants for both the cross-sectional and cohort studies						
Data Collection						
Cross-sectional surveys (3 sites)						
Follow-up survey for incident events and mortality						
Cohort 1: First follow-up survey for incident events and mortality (3 sites)						
Cohort-1:Second follow-up survey for incident events and mortality (3 sites)						
Cohort-1: Third follow-up survey for incident events and mortality (3 sites)						
Cohort-1:Fourth follow-up survey for incident events and mortality (4 sites)						
Cohort-2: First follow-up survey for incident events and mortality (3 sites)						
Data entry and data cleaning						
Analysis						
Data analysis and reporting						
Audits and reporting						
Monitoring and evaluation						
Monitoring						
Process evaluation						
Outcome evaluation						
Obtain Support for Expansion of Surveillance Model						

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Comment [r1]: Changed the timeline to 2013

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SIGNATURE PAGE

The signatures below constitute approval of this protocol by the signatories and provide the necessary assurances that this study will be conducted according to all requisites of the protocol including all statements regarding confidentiality.

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