Prevention of Type 2 Diabetes amongst South Asians with central obesity and prediabetes

iHealth-T2D

Clinical Study Protocol

Prepared by:	**Title:**	**Signature:**	**Date:**
John Chambers	Professor in Cardiovascular Epidemiology		
Ninha Silva	Project Manager		
Approved By:	**Title:**	**Signature:**	**Date:**

History of Changes		
Version	**Date**	**Reason for Changes**
1	**1st March 2016**	
2	**1st of November 2016**	**Reduction of waist circumference reduction in Sri Lanka, in order to allow the lifestyle intervention to the 20% of Sri Lankans with the highest levels of central obesity**

1. PROTOCOL OUTLINE

Title: Prevention of Type 2 Diabetes amongst South Asians with central obesity and prediabetes

Short name/acronym: iHealth-T2D

EudraCT number:	2016-001350-18
Ethics Reference number:	**16/WM/0171**
Chief Investigator (CI):	Professor John Chambers
Co-Investigators:	
Devki Devi Foundation	Dr Sujeet Jha
University of Colombo	Dr Prasad Katalunda
University of Kelaniya	Prof Raj Wickremasinghe
University of Surrey	Prof Graham Cookson
London North West Healthcare NHS Trust	Prof Jaspal Singh Kooner
Institute of Health Policy	Dr Ravindra Rannan-Eliya
University of Amsterdam	Dr Karien Stronks
University of Oulu	Prof Marjo-Riitta Jarvelin
Punjab Institute of Cardiology	Dr Sajjad Ahmed
Services Institute of Medical Sciences	Dr Khadija Irfan Khawaja

Study Coordination:
For general queries, supply of study documentation, and collection of data, please contact:

Study Coordinator: Professor John Chambers
Address: Department of Epidemiology and Biostatistics, Imperial College London, School of Medicine, St Mary's Campus, Paddington, W2 1PG
Email: john.chambers@imperial.ac.uk
Tel: (+44) 7866 365 776

Project Manager: Miss Ninha Silva
Address: Department of Epidemiology and Biostatistics, Imperial College London, School of Medicine, St Mary's Campus, Paddington, W2 1PG
Email: ninha.silva@imperial.ac.uk
Tel: (+44) 020 7594 1530

Sponsor:
Imperial College London is the main research Sponsor for this study. For further information regarding the sponsorship conditions, please contact the Head of regulatory Compliance at:

Joint Research Compliance Office
5L10C, 5th Floor Lab Block
Charing Cross Hospital, Fulham Palace Road
London, W6 8RF
Tel: (+44) 203 311 0204
Fax:(+44) 203 311 0203

Funder:
This project has been funded by the European Commission, under H2020 EU Research and Innovation programme:

European Commission
DG Research & Innovation
E4 Non-communicable diseases and the challenge of healthy ageing
CDMA 02/004
B-1049 Brussels/Belgium

This protocol describes the iHealth-T2D study and provides information about procedures for entering participants. Every care was taken in its drafting, but corrections or amendments may be necessary. These will be circulated to investigators in the study. Problems relating to this study should be referred, in the first instance, to the Chief Investigator. This study will adhere to principles outlined in the NHS Research Governance Framework for Health and Social Care (2nd edition). It will be conducted in compliance with the protocol, the Data Protection Act and other regulatory requirements as appropriate.

2. STUDY SYNOPSIS

Title of the clinical trial	Prevention of Type 2 Diabetes amongst South Asians with central obesity and prediabetes
Protocol short title/acronym	iHealth-T2D
Trial phase	Phase Four
Sponsor name	Imperial College London
Chief Investigator	Professor John Chambers
Eudract number	2016-001350-18
REC number	**16/WM/0171**
Medical condition or disease under investigation	Type 2 Diabetes (T2D)
Purpose of clinical trial	Prevention of T2D in South Asian population
Primary Objective	Determine whether intensive lifestyle modification is clinically effective for prevention of T2D amongst South Asians with central obesity or prediabetes, compared to usual care
Secondary Objective	Assess effects on adiposity measures, glucose metabolism and other measures of well-being in the index case and family members
Trial design	60 months study (1 year recruitment and intervention and 3 years follow-up)
Endpoints	Reduction in the incidence of T2D for intensive lifestyle modification vs usual care
Sample Size	3,600
Summary of eligibility criteria	*Inclusion criteria:* Waist circumference≥100cm **OR** HbA1c≥6.0% South Asian, Male or Female, aged 40-70 years *Exclusion criteria*: Known type 1 or 2 diabetes, fasting glucose≥7.0 mmol/L or HbA1c ≥6.5%; normal or underweight (body mass index<22kg/m^2); pregnant or planning pregnancy; unstable residence or planning to leave the area; serious illness.
Maximum duration of treatment of a subject	1 year

3. GLOSSARY OF TERMS

AE	Adverse Event
CI	Chief Investigator
CHW	Community Health Worker
CRF	Case Report Form
DMC	Data Monitoring and Ethical Committee
GMP	Good Manufacturing Practice
ICH GCP	International Conference on Harmonisation- Good Clinical Practice
ICMJE	International Committee of Medical Journal Editors
IFCC	International Federation of Clinical Chemistry
IGT	Impaired Glucose Tolerance
JRCO	Joint Research Compliance Office
MHRA	Medicines and Healthcare Products Regulatory
NGSP	National Glycohemoglobin Standardization Program
REC	Research Ethics Committee
QA	Quality Assurance
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SOP	Standard Operating Procedure
T2D	Type 2 Diabetes
TMG	Trial Management Group
TSC	Trial Steering Committee

Imperial College London

iHEALTH T2D

TABLE OF CONTENTS

[Appendices provided to REC as separate project documents in IRAS]

BACKGROUND AND RATIONALE OF THE STUDY

4.1 Importance of the Type-2 diabetes in South Asians

The International Diabetes Federation reports that the number of people with Type-2 diabetes (T2D) will rise from 382 million to 592 million between 2013 and 2035. Type-2 diabetes is the fifth leading cause of death worldwide,[1] and a major contributor to development of coronary heart disease, stroke, peripheral vascular disease and end-stage renal failure.[2]

South Asians, who represent one-quarter of the world's population, are at high risk of type-2 diabetes. India alone has ~56 million people with T2D, the second highest number in the world. Conservative estimates based on population growth, ageing and rates of urbanisation show that T2D cases in India will increase to ~100 million by 2030.[3] T2D prevalence is currently ~9% in rural India, ~18% in urban India,[4] and ~22% amongst Indians living in Europe (compared to ~6% among Europeans).[5] Similar patterns are observed among South Asians in Pakistan, Bangladesh, and Sri Lanka.[6]

Diabetes represents a major and growing threat to health and well-being among South Asians, as they migrate from rural to urban areas, and in regional settings around the world. Though diabetes among South Asians is more prevalent among the affluent,[22] recent data show that diabetes rates are rapidly rising among low and middle income South Asians,[27,28] who are also more susceptible to diabetes complications due to reduced access to quality healthcare in these settings.[29] An additional health burden is the earlier age of onset of T2D among South Asians. Diabetes prevalence is ~14 times higher in South Asian than in European children,[30] substantially increasing lifetime burden of disease and its complications. Diabetes poses a massive clinical, economic and social burden among South Asians. The economic disparities within India, Pakistan, Bangladesh, and Sri Lanka, combined with scarcity of adequate healthcare and low education status in large numbers of the population, continue to present a major obstacle in reducing the burden of diabetes in South Asian countries. T2D also places a heavy burden in the health expenditures of European countries to which South Asians have emigrated in large numbers, notably UK, France, Germany, Netherlands and Sweden.

4.2 Lifestyle modification to prevent T2D

Studies in European populations show that intensive lifestyle modifications comprising increased physical activity, dietary change and weight loss is associated with a 30-60% reduction in the incidence of T2D amongst people identified to be at high risk based on the presence of impaired glucose tolerance (IGT, defined as fasting glucose 6.0-6.9 mmol/L or post load glucose 7.8-11.0 mmol/L during an oral glucose tolerance test) and overweight (BMI>25kg/m^2).[9,10]

Few studies have investigated strategies for screening and lifestyle modification for prevention of T2D amongst South Asians. The Indian Diabetes Prevention Program (IDPP) reports a 28% reduction in the risk of T2D after intensive lifestyle modification amongst South Asians.[11] However, the IDPP was limited to South Asians with IGT, from urban environments, and participants were predominantly men (80%) from well-educated backgrounds. Furthermore, approaches to intensive lifestyle modification that rely solely on IGT for identification of high-risk individuals involves measurement of fasting and post-load glucose levels, an expensive, resource-intensive process, requiring high expertise, consumables and specific equipment.[12] As a results of these major obstacles, lifestyle intervention has not been widely implemented, especially in low-middle income regions.

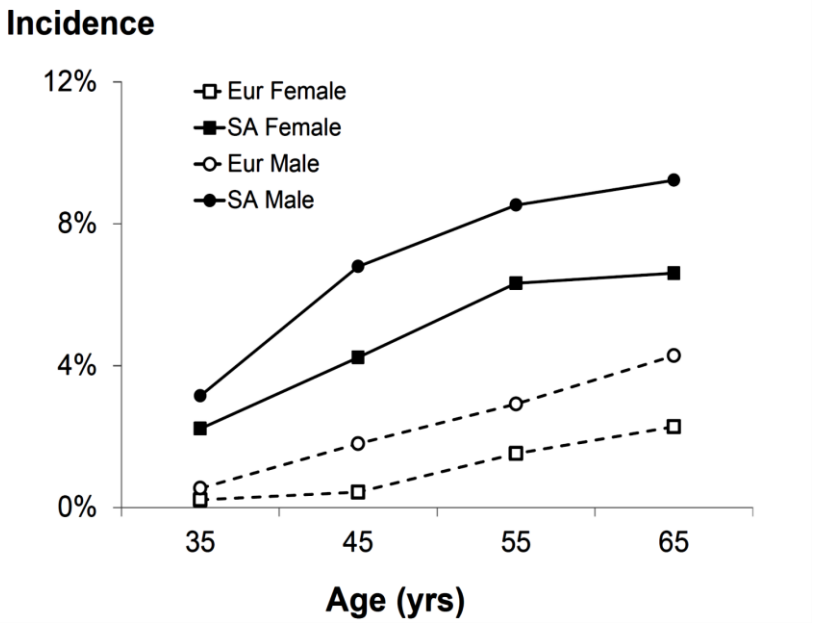
There are 4 studies in progress to investigate strategies of lifestyle modifications for prevention of T2D amongst South Asians (D-CLIP, K-DPP, PDPP, NCT01570946).[13-16] Each have individual strengths, but also potential limitations that may limit equitability, generalizability, scalability and impact on T2D, especially amongst South Asians in low-middle income countries on the Indian subcontinent. These include: i. use of screening tools that are resource intensive (e.g. oral glucose tolerance test) or that are unvalidated for prediction of incident T2D; ii. rely on intensive interventions administered to individuals or use modern technologies that are not equitably

available; iii. have modest scale, thus limiting the robustness of findings and benefit in subgroups; iv. are conducted in a narrow range of geographic locations. There is thus a paucity of evidence to inform prevention of T2D that is effective, efficient and sustainable among South Asian. This is a health inequality that urgently needs to be addressed.

Identifying South Asians at risk of T2D: the London Life Sciences Population (LOLIPOP) study

To investigate new strategies for prediction of T2D amongst South Asians, we have established the LOLIPOP study.[17-19] LOLIPOP is a prospective, population based cohort of 18,606 South Asians and 9,766 European white men and women, aged 35-75 years recruited from the lists of 58 general practitioners in West London (2003-8). After mean 8.4 years' follow-up, we identified 1,554 new cases of T2D in South Asians and 296 amongst Europeans, demonstrating a 3.4 fold (95% CI 3.2-3.6) higher incidence of T2D amongst South Asians than Europeans (**Figure 4.1**). The increased risk of T2D is particularly striking in young South Asians, amongst whom the incidence of T2D is >10 fold higher than in Europeans.

Figure 4.1. 5yr incidence of T2D amongst South Asians (SA) and Europeans (Eur) in LOLIPOP



Results of LOLIPOP enable a well powered, prospective evaluation of risk factors and predictors of incident T2D amongst South Asians. Our results identify HbA1c as highly predictive biochemical tool for identification of high-risk South Asians (**Figure 4.2**). HbA1c achieves better discrimination for T2D than fasting glucose and other single-sample measures of glucose metabolism (**Table 4.2**). In addition, HbA1c has the advantage of being a non-fasting assay, which is simpler and cheaper to administer than an oral glucose tolerance test. These make HbA1c well suited for community-wide and opportunistic screening.[20]

Amongst anthropometric and non-invasive measures, we find that waist circumference is the best predictor of incident T2D in South Asians. Waist circumference achieves better discrimination than body mass index or waist-hip ratio as quantified by AUC (**Table 4.1**). Waist circumference also performs superiorly to the only composite non-invasive risk scores developed for identification of T2D in South Asians (the Indian Diabetes Risk Score). Waist circumference≥100cm identifies ~50% of South Asian men and women in the UK who will develop T2D (**Table 4.2**). T2D is closely associated with waist circumference amongst South Asians on the Indian subcontinent where waist circumference ≥100cm identifies 38% of rural and 45% of urban South Asians with T2D (**Figure 4.3**), and is equally sensitive in men and women. Waist circumference is a simple, readily available

clinical measure of adiposity that is well-suited for use as a tool for community-wide risk stratification, especially in low-middle income countries. Potential advantages include: i. low cost; ii. simple, readily available tool, iii. easy training and iv. high acceptability. Potential limitations though include lower discrimination (AUC) of T2D risk, which may reduce predictive performance.

HbA1c and waist circumference provide complementary information for the identification of South Asians at risk of T2D. Together these measures identify ~70% of South Asians who will go on to develop T2D; if harnessed in an efficient and effective intervention, these measures offer the potential for a major impact on the burden of T2D in South Asians.

These observations provide a strong, evidence-based rationale for the current project in which we will determine the clinical utility and cost-effectiveness of HbA1c and waist circumference for identification of South Asians at high risk of T2D, to enhance scalable implementation of lifestyle modifications and improve health.

Table 4.1. Continuous traits as predictors of incident T2D amongst South Asians in the LOLIPOP study.

Risk factor	AUC
HbA1c	0.74
Fasting glucose	0.72
Fasting insulin	0.68
HOMA-IR	0.67
Waist circumference	0.66
Body mass index	0.64
Waist hip ratio	0.64
Physical inactivity	0.54
Indian Diabetes risk score	0.63

Figure 4.2. 5yr incidence of T2D amongst South Asians in the LOLIPOP study stratified by baseline HbA1c. ADA and WHO thresholds for high risk are shown.

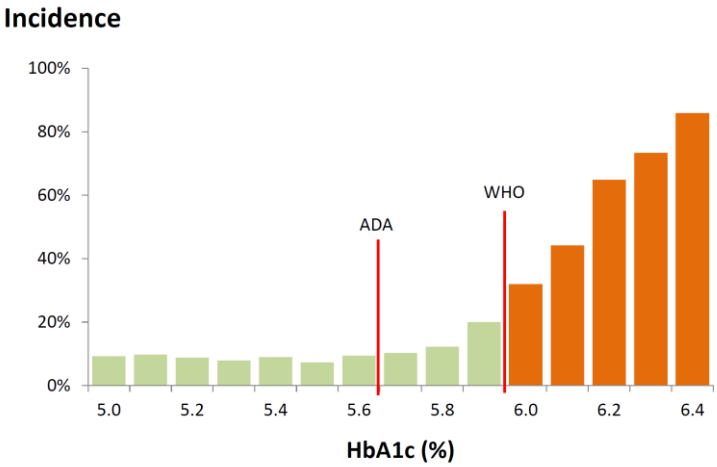
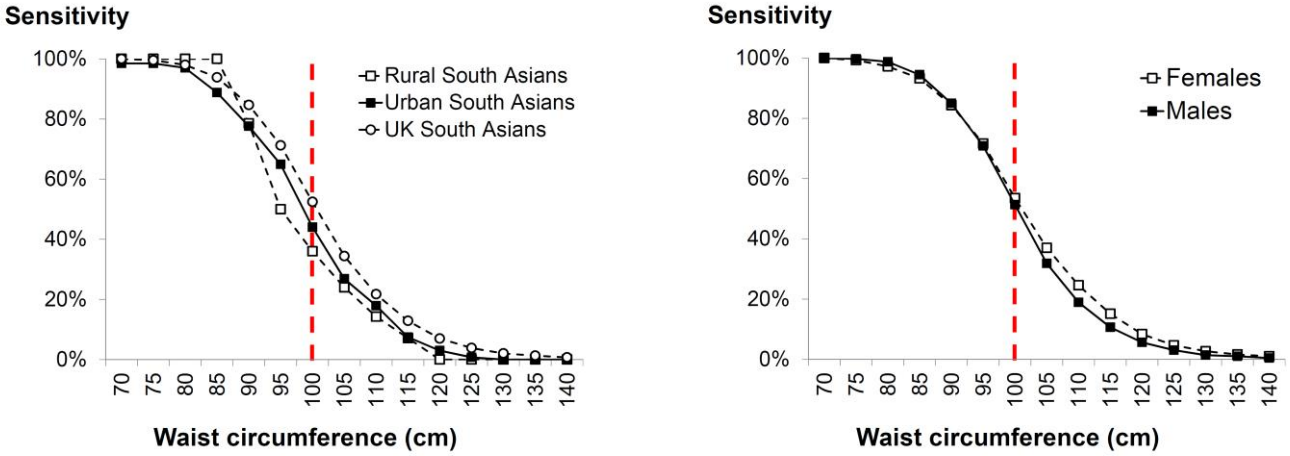


Table 4.2. Risk factors for incident T2D (5 years) amongst South Asians in the LOLIPOP study.

Risk factor	Prevalence	T2D incidence	Sensitivity	RR for T2D
Biochemical				
Fasting glucose ≥6.1mmol/L (WHO)	5.0%	55.6%	19.3%	6.66 (4.89-9.07)
HbA1c ≥6.0% (WHO)	16.3%	68.4%	35.0%	13.9 (10.4-18.6)
Anthropometric				
Body mass index >28 kg/m^2 (WHO)	17.0%	30.1%	32.6%	2.35 (1.96-2.82)
Waist-hip ratio (M>1.0, F>0.9)	28.0%	27.1%	46.2%	2.21 (1.88-2.60)
Waist: M or F ≥100cm	28.9%	31.3%	49.6%	2.56 (2.21-3.06)
Other measures				
Physical inactivity (<150mins/wk)	43.9%	19.7%	35.3%	1.74 (1.40-2.18)

Figure 4.3. Sensitivity of waist circumference for identification of T2D amongst South Asians in rural and urban regions of the Indian subcontinent (DDF) and amongst South Asians in the UK (LOLIPOP) in the left panel, and amongst South Asian men compared to women (right panel). Results show that sensitivity for identification of T2D is high for waist≥100cm in all three environments and in both genders.



4.3 Involving the family in lifestyle modification amongst South Asians

South Asians typically live together as extended families, in a single household.[23] Many behaviours relevant to healthy lifestyle take place within the family home, including meal preparation, communal eating and use of recreational time. These identify family environment as an important determinant of metabolic health, a hypothesis supported both by the clustering of obesity and T2D in South Asian families, and by recent studies which show that lifestyle intervention which targets the family environment is more effective at achieving weight loss amongst people with obesity and IGT than conventional approaches.[24,25]

We have implemented family-based approaches to lifestyle intervention for health promotion amongst UK South Asians with central obesity. The intervention is closely based on established, successful protocols for prevention of T2D through weight loss, but has been culturally adapted for South Asians (e.g. detailed food composition tables that capture customary diet, and translation of materials into relevant languages). Family members of the index obese South Asian are strongly encouraged to join the program, in particular young family members (>18 years old) and the family cook(s). The goal is for the family to take joint responsibility for change to a healthy lifestyle, supporting and guiding the obese index case in making healthy choices, and maintaining long-term engagement in the lifestyle intervention program.

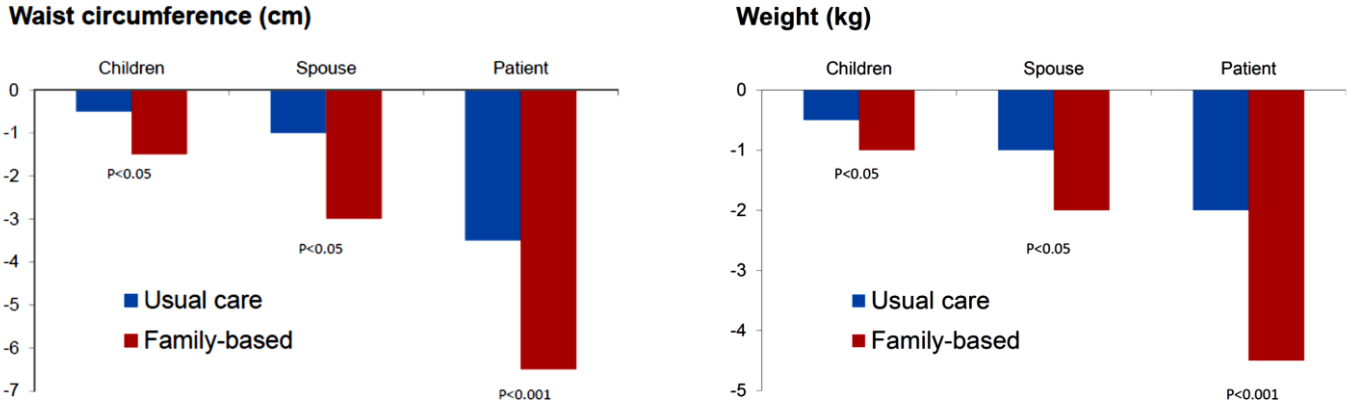
The target is for the index case to avoid new onset of T2D as defined by the primary endpoint, through a combination of reduced calorific intake, lower consumption of fat and refined sugars, and increased physical activity (150 minutes of moderate physical activity per week). Lifestyle modification is delivered over 22 contact sessions (weekly for 3 months, then every 4 weeks for 9 months). The initial session focuses on education around obesity and diabetes. Subsequent sessions focus on implementation of healthy diet and increased physical activity. Nutritional education is focused on cooking methods, portion size, food choices, amount of fat used in cooking and encouraging foods high in dietary fibre.

In our experience (Imperial College London), index cases show an average 6.8±3.6cm reduction in waist circumference, and 4.2±3.2kg weight loss (both P<0.001 compared with usual care, **Figure 1.4**). This is accompanied by reductions in fasting glucose (0.2±0.3mmol/L, P<0.05) and HbA1c (0.2±0.2%, P<0.05). Based on the relationship of waist circumference with incident T2D amongst South Asians in LOLIPOP (6.4% [95%CI 5.5-7.3%] increase in risk of T2D per 1cm increase in waist circumference), we predict that family-based intervention could reduce the incidence of T2D by ~42% in South Asians with central obesity. Furthermore, our pilot studies suggest additional

health gains amongst the wider family, including children who represent the next generation of people at risk of T2D (**Figure 4.4**).

These observations provide the rationale for our choice of a family based approach to lifestyle modification amongst South Asians, and the justification for evaluating the potential health benefits of lifestyle modification amongst both the index case and their family members.

Figure 4.4. Reduction in waist circumference and weight in index cases and relatives under family-based intervention (N=102 index cases) vs individually administered care (N=56 index cases).



5. AIMS OF THE RESEARCH

Our general goal is to identify approaches to risk stratification and health promotion through lifestyle modification that are acceptable, effective and efficient for prevention of T2D in South Asian communities from diverse settings.

The specific aims of the proposed iHealth-T2D study are:

1. Determine whether intensive lifestyle modification vs usual care reduces risk of T2D (primary endpoint) amongst South Asians with i. central obesity; ii. prediabetes and iii. overall (with central obesity and / or obesity).

2. Investigate secondary endpoints, including health gains in family members. Identify social, demographic and environmental factors influencing primary and secondary endpoints.

3. Carry out a health economic analysis of lifestyle modifications vs usual care for prevention of T2D on the Indian subcontinent and Europe. Quantify the cost-effectiveness of screening by waist circumference vs HbA1c.

5. STUDY DESIGN

This is a multi-centre, cluster randomised clinical trial to compare intensive lifestyle modification vs usual care for prevention of T2D amongst non-diabetic South Asians with central obesity and / or prediabetes. The study comprises one year intervention and 3 years follow-up. The study design is shown in **Figure 6.1** (CONSORT diagram).

We will recruit 3,600 South Asian men and women aged 40-70 years with i. central obesity (waist≥100 cm) and/or ii. prediabetes (HbA1c 6.0-6.4%) to the study (**Index cases**). Recruitment will be from the Indian subcontinent (India, Pakistan, Sri Lanka) and Europe (UK). Index cases will receive either i. intensive lifestyle modification (N=1,800); or ii. usual care (N=1,800). Intensive lifestyle modification follows clinically accepted, evidence based strategies to achieve >7% reduction in weight through improved diet and increased physical activity, and is delivered as 9 face-face and 13 telephone contact sessions over 12 months. Index cases are the focus for the intervention, but lifestyle modification encourages the whole family to adopt healthy living. Usual care group will comprise one diabetes prevention session and written material.

Index cases will be followed for three years to identify new-onset T2D (primary endpoint, HbA1c≥6.5%). Secondary outcome measures will include a range of clinical, lifestyle and biochemical measures. Assessments of adiposity will also be made amongst available, consenting adult relatives of index cases in the intervention group (**Relatives)**, to describe the potential benefit of providing health promotion to the index case in the wider family.

The primary analyses will determine the clinical and cost-effectiveness of intensive lifestyle modification vs usual care for prevention of T2D amongst South Asians with i. central obesity; ii. prediabetes or iii, overall. Secondary analyses will address behavioural, clinical, and biochemical measures similarly. All analyses will be intention to treat. Health economic analyses will take account of costs incurred by the government, and participants. Effectiveness will be measured in terms of screening numbers needed to identify one case of 'high risk' for developing diabetes, and numbers needed to treat to prevent or delay one case of diabetes.

Summary of the iHealth-T2D study

Setting	120 recruitment sites (N=30 each in India, Pakistan, Sri Lanka and UK).
Cluster randomisation	1:1 allocation of sites to active group (N=60) or control group (N=60), stratified by country and socio-economic characteristics
Sample size	Total N=3,600 index cases (15 men and 15 women at each of the 120 recruitment sites) and their available consenting adult relatives.
Ethics	Institutional review board approval will be obtained before starting Informed consent will be obtained from each participant

Study entry criteria for Index cases

Inclusion criteria:	Waist circumference≥100cm OR HbA1c≥6.0% South Asian, Male or Female, and age 40-70 years
Exclusion criteria:	Known type 1 or 2 diabetes, fasting glucose≥7.0 mmol/L or HbA1c ≥6.5%; normal or underweight (body mass index<22kg/m2); pregnant or planning pregnancy; unstable residence or planning to leave the area; serious illness.

Study entry criteria for Relatives

Inclusion criteria:	Age >18 years and living in the same household as an Index case receiving intensive lifestyle modification
Exclusion criteria:	Known type 1 or 2 diabetes. Serious illness.

Intervention

Active group sites:	Intensive lifestyle modification as 9 face-face and 13 telephone contact sessions over 12 months
Control group sites:	Usual care. Single health promotion session with written material.
Follow-up	Annual follow-up for 3 years (i.e. 12 months, 24 months, 36 months) HbA1c, waist circumference, weight and other health data Waist circumference and weight measurements in adult (age>18-75 yrs) family members
Primary endpoint	New onset T2D in the index case defined as • HbA1c≥6.5% or • Physician diagnosis and on medication for diabetes.

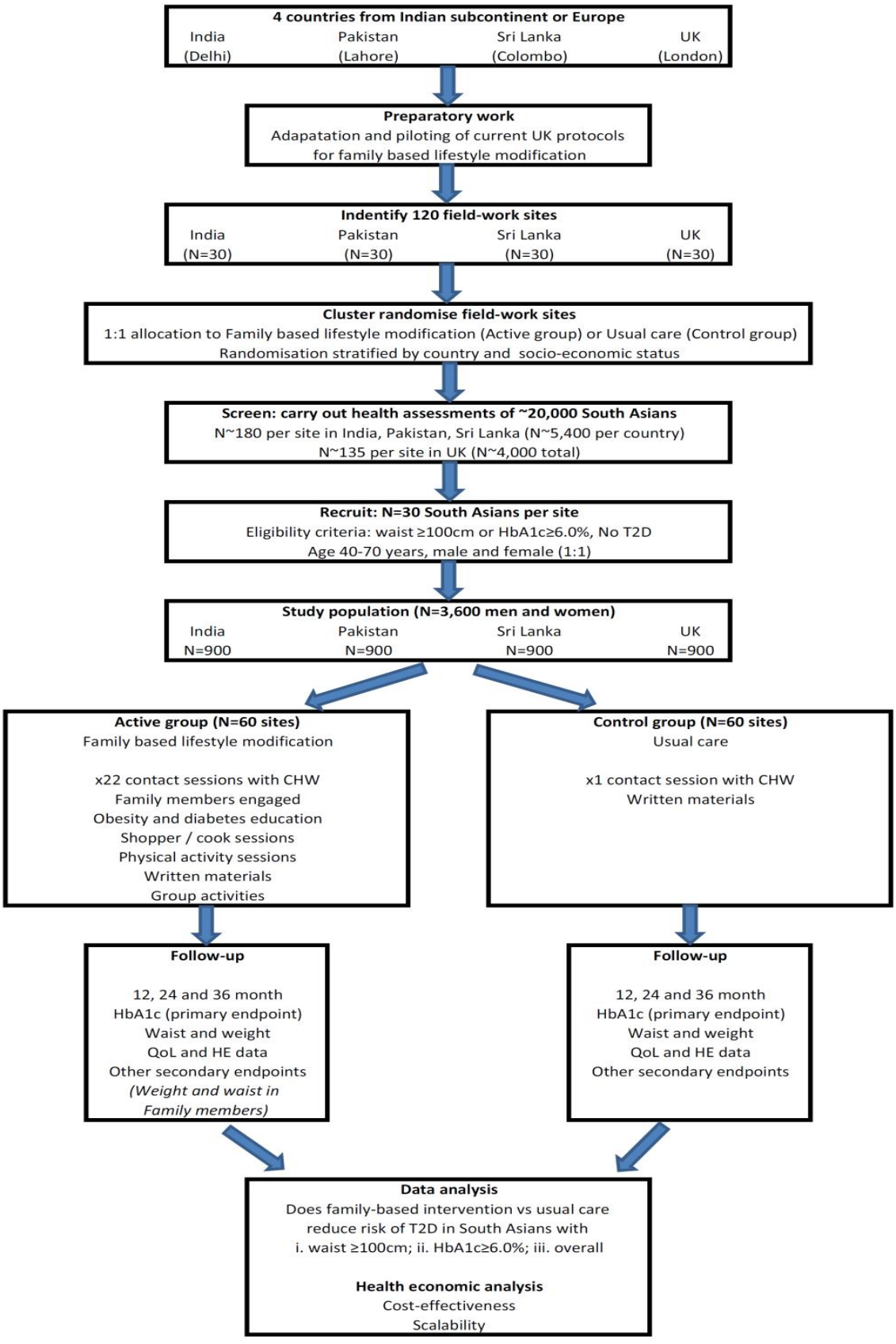
Secondary endpoints

Index cases	• Physical: waist circumference, weight and blood pressure • Lifestyle: cigarette and alcohol intake, physical activity. • Biochemical: fasting glucose and lipids • Psychosocial measures: anxiety, depression.
Family members:	Waist circumference and weight

Analysis and reporting

Approach	Intention to treat with pre-specified analysis plan
Primary analysis:	T2D incidence for intervention vs usual care in 3 groups: 1. South Asians with central obesity 2. South Asians with prediabetes 3. Overall, i.e. South Asians with central obesity and / or diabetes Statistical significance: P<0.017 (i.e. P<0.05 corrected for 3 groups)
Secondary analyses:	Waist circumference, weight, glucose and lipids in index case. Health gains in adult family members, such as weight loss
Health economic	Cost effectiveness
Reporting	Register clinical trial Report design, methods and findings in open access format Disseminate to local and national experts and policy makers

Fig.6.1 CONSORT diagram summarising study design.



7. PARTICIPANT ENTRY

7.1. Index cases

We will recruit South Asian men and women aged 40-70 years with i. central obesity (waist≥100 cm) and/or ii. prediabetes (HbA1c 6.0-6.4%) to the study (index cases). Recruitment will be from the Indian subcontinent (India, Pakistan, and Sri Lanka) and Europe (UK). There will be 900 Index cases recruited in each of the 4 countries, to provide a total of 3,600 Index cases. To identify 3,600 people meeting these criteria, we expect to screen ~20,000 people. The approaches to screening and recruitment are described in detail in section 9.1.

Inclusion and exclusion criteria for index cases

Inclusion criteria:

- Waist circumference≥100cm **OR** HbA1c≥6.0%
- South Asian, Male or Female, and age 40-70 years

Exclusion criteria:

- Known type 1 or 2 diabetes
- Fasting glucose≥7.0 mmol/L or HbA1c ≥6.5%
- Normal or underweight (body mass index<22kg/m^2)
- Pregnant or planning pregnancy
- Unstable residence or planning to leave the area
- Serious illness
- Lack of capacity to consent

South Asians will be identified as people of self-reported South Asian ancestry who were born in the Indian subcontinent, or who have all 4 grand-parents born in the Indian subcontinent.

7.2. Relatives

We will also invite the adult relatives living in the same household as one of the 3,600 index cases to participate in a focussed, limited evaluation of the potential health benefits for the wider family of providing intensive lifestyle modification to the index case.

Inclusion and exclusion criteria for relatives

Inclusion criteria:

- South Asian, Male or Female, and age>18 years
- Living in the same household as an index case receiving intensive lifestyle modification.

Exclusion criteria:

- Known type 1 or 2 diabetes
- Serious illness
- Lack of capacity to consent

7.3. Withdrawal of subjects

All participants in the study will be informed upon recruitment that they have the right to withdraw from the study at any time for any reason. Should a patient decide to withdraw from the study, all efforts will be made to report the reason for withdrawal as thoroughly as possible.

The investigator will consider withdrawing participants from the study in the following situations:

- Occurrence of pregnancy after recruitment or during study participation
- If participant missed two or more consecutive clinical visits
- The investigator or/and GP believes it is in the best interest of the subject

Participants who wish to withdraw from the study will be asked to confirm whether they are still willing to provide trial-specific data provided up to the last visit, and/or data collected as per routine clinical practice up to the last visit.

8. ADVERSE EVENTS

8.1. Definitions

Adverse Event (AE): any untoward medical occurrence in a patient or clinical study subject. An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, whether or not considered related to the trial protocol.

Serious Adverse Event (SAE): any untoward and unexpected medical occurrence or effect that:

- Results in death
- Is life-threatening – *refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe*
- Requires hospitalisation or prolongation of existing inpatients' hospitalisation – "Hospitalisation" means any unexpected admission to a hospital department. It does not usually apply to scheduled admissions that were planned before study inclusion or visits to casualty (without admission).
- Results in persistent or significant disability or incapacity
- Is a congenital anomaly or birth defect

Medical judgement will be exercised in deciding whether an AE is serious in other situations. Important AEs that are not immediately life-threatening or do not result in death or hospitalisation but may jeopardise the subject or may require intervention to prevent one of the other outcomes listed in the definition above, will also be considered serious.

8.2. Reporting procedures and responsibilities

There are no expected Adverse Events throughout this study. In the unexpected occurrence of an AE, the adverse event will be reported. Depending on the nature of the event the reporting procedures below will be followed.

8.2.1. Adverse Events (AEs)

All such events, whether expected or not, will be recorded.

8.2.2. Serious Adverse Events (SAEs)

An SAE form will be completed and faxed to the Chief Investigator within 24 hours. New onset diabetes, and hospitalisations for elective treatment of a pre-existing condition do not need reporting as SAEs.

All SAEs will be reported to the Sponsor where in the opinion of the Chief Investigator, the event was:

- 'related', ie resulted from the administration of any of the research procedures; and
- 'unexpected', ie an event that is not listed in the protocol as an expected occurrence

Reports of related and unexpected SAEs will be submitted to the REC by the Chief Investigator or Sponsor within 15 days of the Chief Investigator becoming aware of the event. The report will be submitted using the SAE report form for non-CTIMPS study, available from the HRA website.

9. TRIAL PROCEDURES, ASSESSMENT AND FOLLOW-UP

9.1. Recruitment

We will recruit 3,600 South Asians men and women, aged 40-70 years, who have central adiposity (waist circumference≥100cm) or prediabetes (HbA1c≥6.0% and <6.5%) to the study [**Index cases**]. We will also invite the adult relatives of Index cases receiving intensive lifestyle modification to take part [**Relatives**].

Identification and selection of recruitment sites

Participants will be recruited from 120 sites divided equally between India, Pakistan, Sri Lanka and UK (ie 30 recruitment sites per country, **Appendix A**). At each site we will recruit 30 South Asians (15 male, 15 female) meeting the study entry criteria, to provide a total sample of 3,600 South Asians with central obesity and / or prediabetes in the study. On the Indian subcontinent recruitment sites will be based in a range of socio-economic and geographic settings, to increase the generalizability of the findings. Locations have been identified based on the knowledge and advice of local experts and available administrative data for the region. In the UK, recruitment sites will be GP surgeries in London serving populations with a high proportion (>25%) of South Asians. The socio-demographic and geographic characteristics of potential recruitment-sites will be documented using national administrative data (**Table 9.1**), under the direction of Health Economists from the partner organisations at University of Surrey (UK) and the Institute of Health Policy (Sri Lanka).

Table 9.1: Sources of national administrative data used for characterisation of sites, and stratified cluster randomisation

Country	Data Source
UK	Office for National Statistics
India	Indian Ministry of Home Affairs
Pakistan	Lahore Journal of Policy Studies; Pakistan Bureau of Statistics
Sri Lanka	Department of Census and Statistics of Sri Lanka

Cluster randomization:

The clinical trial will compare Intensive lifestyle intervention with usual care. This can only be done in an unblinded fashion (participant and provider). We will therefore use cluster randomisation of recruitment sites rather than individual participant randomisation) to allocate treatment group. Cluster randomisation reduces the risk of resentful demoralisation and Hawthorne effect (contamination) during unblinded interventions. The 120 selected recruitment sites will be randomised with 1:1 allocation to either: i. Intensive lifestyle modification (active group, N=60); or ii. Usual care (control group N=60). Randomisation will be stratified by 2 levels: i. Country: India, Pakistan, Sri Lanka, UK (30 sites per country); ii. Socio-economic: top, middle or bottom tertile of estimated average household income, amongst the 30 sites identified in the respective country (10 sites in each tertile per country). Cluster randomisation will be carried out using random number generation and a simple algorithm implemented in a computer package. Randomisation will be done before recruitment commences.

Screening through local health assessments
At each recruitment site we will invite South Asian men and women aged 40-70 years from the local community to attend for a health assessment. In the UK, participants will be approached by post, from the practice lists of collaborating general practitioners. In South Asia we will hold discussions with community leaders and open meetings to identify suitable approaches for engaging local communities in the project. We anticipate distributing knowledge of the project and inviting people to attend for screening through trusted sources of health information (e.g. health centres, physicians and health care providers, grass root level non-physician health workers, accredited social health activists and volunteer groups). This may be supplemented by postal invitation through electoral registers where these are available. People will be encouraged to discuss the project with neighbours and friends to help widen engagement.

The screening health assessment will last ~30 minutes and will comprise:

1. Informed consent for screening
2. Screening questionnaire (**Appendix B**)
3. Physical measurements including waist circumference, as well as height and weight for calculation of body mass index, and blood pressure.
4. Collection of a non-fasting venous blood sample (**Table 9.2**) for measurement of HbA1c as a study entry criterion, and storage of serum and whole blood for future molecular epidemiological research into biomarkers for metabolic and cardiovascular health

Health assessment centres will be set up at easily accessible location within walking distance of the target population, in community centres and health centres. To ensure we engage a wide segment of society, the health assessment centres will be carried during the both the working day and during the evening and at weekends. All people attending for a health assessment will be given a printed report of their results, along with guidance on their interpretation and recommendations for action. People with newly diagnosed T2D will be offered a clinical consultation with a medical member of the project team.

Table 9.2: Blood samples to be collected at screening, enrolment and follow-up visits.

	Clinical bloods		**Research bloods**				**Total volume**
	HbA1c	***Serum***	***Whole blood***	***Serum***	***Plasma***	***RNA***	
BD tube	Lavender (EDTA)	Gold (SST)	Lavender (EDTA)	Gold (SST)	Green (LiHeparin)	PaxGene	
Blood draw	2mls	5mls	4mls	5mls	4.5mls	8.5mls	
UK	1	1	1	2	2	1	38.5mls
India	1	1	1	2	0	0	21mls
Pakistan	1	1	1	2	0	0	21mls
Sri Lanka	1	1	1	2	0	0	21mls

Enrolment of index cases
South Asians reaching the study entry criteria based on the initial health assessment will be invited to attend an enrolment (baseline) visit at a dedicated research clinic where they will be seen by one of the study research nurses. They will be asked to attend in the fasting state (overnight), and the appointment is expected to last ~60 mins. This assessment will comprise:

1. Informed consent for enrolment
2. Enrolment questionnaire (**Appendix B**)
3. Physical measurement, including waist circumference, body mass index and blood pressure.
5. Physical activity: Global Physical Activity Questionnaire (GPAQ, **Appendix C**)
6. Health-related quality of life questionnaire (EQ-5D-5L, **Appendix D**)
7. Collection of a fasting venous blood sample (**Table 9.2**) for measurement of HbA1c as a study entry criterion, and storage of serum and whole blood for future molecular epidemiological research.

The information collected at the enrolment visit will be used to reconfirm eligibility. Based on repeat measures performed in our population studies we expect ~10% of potential participants to be no longer eligible when reassessed. The primary reasons for this will be waist circumference <100cm, or HbA1c<6.0 or ≥6.5% at repeat measure. South Asians who continue to meet the study eligibility criteria will continue to the intervention phase of the study.

Trial procedures:
Consent. All participants will be asked to give written consent. Information sheets and consent forms will be available in the major South Asian languages as well as videos describing the study in the relevant languages. Multilingual translators will be available as required. People unwilling or unable to provide consent will be excluded.

Physical measurements. Waist circumference will be measured over bare skin at the midpoint between the lower margin of the last palpable rib and the top of the iliac crest. Hip circumference at the level of the greater trochanters. Waist and Hip measurements will be measured three times and the average calculated. Our unpublished data shows that this reduces the co-efficient of variation for waist measurements from 1.5% to 0.6%; for people with central obesity this corresponds to a reduction in the SD for the difference between paired measurements of waist, from ~1.8cm to ~0.8cm. Weight will be measured in light clothing using portable digital scales accurate to 0.1kg, and height using a portable stadiometer.

HbA1c assays. HbA1c will be measured using an assay that is not affected by haemoglobinopathies (http://www.ngsp.org/interf.asp), Assays will be performed in local laboratories that undertake robust internal and external QC, meet IFCC standards and are part of the IFCC network of laboratories (**Table 9.3**). All participating laboratories have agreed to provide their internal QC and external QA data on a monthly basis during the course of the study for assessment of laboratory performance.

Table 9.3: Laboratories providing HbA1c assays for the iHealth-T2D study.

COUNTRY	LABORATORY	ADDRESS	MAIN CONTACT
UNITED KINGDOM	TDL Ealing Hospital	Ealing Hospital, Uxbridge Road, Southall, Middlesex UB1 3HW	Dr Francis Geoghegan frank.geoghegan@nhs.net
INDIA	Max Labs 24x7	B1, Max Super Speciality Hospital, 1 Press Enclave Road, Saket, New Delhi-110017	Dr.Dilip Kumar dkumar@maxhealthcare.com
PAKISTAN	Pathology Laboratory	Punjab Institute of Cardiology, Ghous-ul-Azam (Jail) Road, Lahore	Mr Muhammad Ramzan 0429920305165 (Ext209)
SRI LANKA	Asiri Hospital Holdings PLC	Nr 181, Kirula Road, Colombo 05	Rosham Palihawadana roshanp@asiri.lk

Feasibility and delivery of recruitment targets

Recruitment will continue at each recruitment site until there are 15 male and 15 female consenting participants meeting the study entry criteria after both the initial health assessment and the baseline assessment during recruitment. Our estimates of the effort and resources needed to complete recruitment are based on the following observations

- Our extensive population data on the Indian subcontinent and in Europe, indicate that ~25% of South Asians on the Indian subcontinent (~13% in rural areas, up to 35% in urban areas), and ~35% of South Asians in the UK will reach the study entry criteria at the initial health assessment. These will be invited to the enrolment visit.
- Based on our experience of recruiting South Asians to research studies, the simple nature of the intervention proposed and the high level of anxiety in the community concerning obesity and diabetes, we expect ~75% of individuals who have been identified as obese and / or prediabetic at the initial health assessment to then attend the enrolment visit.
- As described above we expect that ~10% of individuals will no longer reach entry criteria when reassessed at the enrolment assessment.

Taking these factors together we expect to carry out health assessments on ~180 South Asians on the Indian subcontinent and ~135 South Asians in the UK, to identify 30 consenting and eligible participants at each recruitment site for inclusion in the study. Across the project as a whole (120 recruitment sites) we expect to carry out short health assessments on ~20,000 South Asians (~5,400 each in India, Pakistan and Sri Lanka, and ~4,000 in the UK) followed by 4,000 enrolment assessments, to deliver the total study sample of 3,600 participants. Study recruitment will be monitored closely, with daily reports to the Project lead and lead investigators to enable remedial action to be taken if necessary, at the earliest opportunity.

9.2. Study intervention

Summary

This study will compare intensive lifestyle modification vs usual care for prevention of T2D amongst participants. Intensive intervention will comprise 22 sessions about lifestyle modifications delivered over 12 months, nine of which are face-to-face clinic appointments and 13 of which are telephone contacts. The programme is delivered by a community health worker, and involves available adult family members. Usual care group will comprise one diabetes prevention session and written material.

Recruitment sites and cluster-randomization

Identification and cluster randomization of recruitment sites is described earlier. In brief, there will be 120 recruitment sites (30 each in India, Pakistan, Sri Lanka and UK), with 30 South Asians recruited at each site with equal numbers of men and women. Recruitment sites are cluster-randomised (1:1) to either: i. Intensive lifestyle modification (active group, N=60); or ii. Usual care (control group N=60). At any given recruitment location, all research participants will receive either active or control intervention as determined by the site's treatment group allocation.

Community health workers

Interventions will be delivered by community health workers who will be provided with structured training in lifestyle modification. Community health workers will be recruited from amongst the local community in which they will be working to ensure natural cultural awareness. The community health workers will be graduates with a biological background. Training of community health workers will be provided by local experts in diabetes, nutrition and exercise, according to the principles and practices described in the study protocol. Community health workers will each be provided with a study workbook detailing the protocols to be followed for implementation of both family lifestyle modification and usual care. The workbook also contains detailed toolkits for promoting healthy diet and increased physical activity in the active group.

Active intervention group: Intensive lifestyle modification

Overview. Intensive lifestyle modification will use validated, evidence based, clinically accepted approaches, derived from published studies of successful lifestyle modification to prevent T2D. The protocols have been culturally adapted for use in South Asian populations (eg to include South Asian rather than European foods and eating habits). In addition, the intervention will take advantage of telephone and group sessions, validated approaches to clinical delivery of lifestyle modification, to optimise cost-effectiveness.

Participants. Lifestyle modification will be provided to the index cases and adult (age>18yrs) family members sharing the same household. All adult family members (who do not have diabetes or other major illness) will be encouraged to take part in lifestyle modification, but participation is voluntary. Where family members do chose to participate in the lifestyle modification, we will ask their permission (ie take consent) to collect and use a limited set of individual level demographic and anthropometric data for the research (**Appendix G**). Consent for use of the data for research is voluntary and will not be required for the family member to participate in the clinical aspects of lifestyle modification for health promotion.

Key objectives. The index case aims to achieve a 7% reduction in body mass index and a 10 cm reduction in waist circumference through improved diet and increased physical activity. **Improved diet** includes attention to appropriate portion size, identifying cooking substitutions to reduce fat, increasing fruit and vegetable consumption, decreasing sugar intake, and reducing alcohol consumption where appropriate. **Increased physical activity** includes finding enjoyable physical activities to pursue regularly, and incorporate physical activity into daily routines. The target is to achieve 150mins of moderate physical activity every week.

Schedule of visits. Lifestyle modification will be delivered over 12 months through 22 contact sessions. Sessions will comprise face-to-face meetings on a one-one basis (**121**, N=5) or in groups (**Group**, N=4), supplemented by telephone contact (**Phone**, N=13). The use of group and telephone contact sessions is clinically validated and highly cost-effective compared to wholly face-face strategies. Session content and timing are summarised below (**Table 9.4**). *All components reflect accepted clinical practice for intensive lifestyle modification to prevent T2D.*

Table 9.4: Summary of schedule of visits

Episode	Visit Type	Week	Duration (min)	Description
1	**Clinic visit 1 [121]**	1	150	Physical measurements of index case and consenting family member; lifestyle data collection; setting targets; discussion and calorie prescription; importance and confidence scale.
2	**Phone call**	2	25	Review problems; reminder and reinforcement of deliverables; setting date for next visit.
3	**Clinic visit 2 [121]**	3	80	Theme: Diet Prescription; physical measurements of index case and consenting family member; lifestyle data collection; importance and confidence scale; setting targets and diet plan.
4	**Phone call**	5	25	Telephone intervention; reminder and reinforcement of deliverables; setting date for next visit.
5	**Clinic visit 3 [Group]**	7	70	Theme: Fats; physical measurements of index case and consenting family member; review of targets; group activities.
6	**Phone call**	9	25	Telephone intervention; reminder and reinforcement of deliverables; setting date for next visit.
7	**Clinic visit 4 [Group]**	11	110	Theme: Carbohydrates; physical measurements of index case and consenting family member; review of targets; group activities.
8	**Phone call**	13	25	Telephone intervention; reminder and reinforcement of deliverables; setting date for next visit.
9	**Clinic visit 5 [Group]**	15	80	Theme: Triggers, food labels and special occasions; physical measurements of index case and consenting family member; review of targets.
10	**Phone call**	17	25	Telephone intervention; reminder and reinforcement of deliverables; setting date for next visit.
11	**Clinic visit 6 [121]**	19	100	Theme: Review; physical measurements of index case and consenting family member; importance and confidence scale; target review; eating plan.
12	**Phone call**	21	25	Telephone intervention; reminder and reinforcement of deliverables; setting date for next phone call.
13	**Phone call**	23	25	Telephone intervention; reminder and reinforcement of deliverables; setting date for next visit.
14	**Clinic visit 7 [Group]**	25	110	Theme: Eating out & Pressures to eat; physical measurements of index case and consenting family member; target review.
15	**Phone call**	28	25	Telephone intervention; reminder and reinforcement of deliverables; setting date for next phone call.

16	**Phone call**	31	25	Telephone intervention; reminder and reinforcement of deliverables; setting date for next phone call.
17	**Phone call**	34	25	Telephone intervention; reminder and reinforcement of deliverables; setting date for next visit.
18	**Clinic visit 8 [121]**	37	80	Theme: Recipe adaptation, sharing positive changes and formation of "buddy system"; physical measurements of index case and consenting family member; target review.
19	**Phone call**	40	25	Telephone intervention; reminder and reinforcement of deliverables; setting date for next phone call.
20	**Phone call**	43	25	Telephone intervention; reminder and reinforcement of deliverables; setting date for next phone call.
21	**Phone call**	46	25	Telephone intervention; reminder and reinforcement of deliverables; setting date for last visit.
22	**Clinic visit 9 [121]**	49	105	Theme: Review; physical measurements of index case and consenting family member; importance and confidence scale.

Resource materials for participants. Index cases and their family members will be provided with a participant handbook ("Participant Handbook for Intervention Group", **Appendix E**) and a non-elastic measuring tape to measure their waist circumference to assess their progress. The handbook contains educational information about the importance of obesity and diabetes, the potential benefits of lifestyle modification, and the key components healthy lifestyle (focused on improved and increased physical activity). The workbook guides the participants through the lifestyle modification sessions with self-monitoring of their lifestyle behaviours, goal setting, goal review and waist circumference.

Meeting locations. Meeting places and times will be chosen with the group to maximise convenience and encourage compliance. Typically, these will be held in community settings. Some sessions will require meeting in public places eg visits to the local shops or for exercise sessions.

Data collection.
A lifestyle intervention case report folder will be completed for each Index case receiving intensive lifestyle intervention (CRF, **Appendix G**). This will record dietary intake through 24h food recall and Food Frequency Questionnaire, Physical activity (by GPAQ), weight loss targets, calorie prescriptions, motivation scores, and weight / waist measurements throughout the duration of the intervention. The CRF will also collect information from consenting relatives. Data from the CRF will be transposed to the study database.

Control Intervention group: Usual care
Participants in the control arm are provided with a single diabetes prevention education session on lifestyle modification and written material ("Participant Handbook for Control Group", **Appendix F**), lasting 30-60 minutes and delivered by the community health worker. Participants are also given a copy of their blood pressure, anthropometric and biochemical measurements collected at baseline, with a recommendation to consult a healthcare provider if the values are abnormal. A structured questionnaire will be used to collect feedback on access, acceptability, equity and satisfaction with the interventions delivered in the lifestyle modification program.

9.3. Follow-up

Summary

All index cases enrolled to the study will be asked to attend follow-up visits with a research nurse at 12, 24, and 36 months. We will follow-up the index cases to:

1. Identify new-onset T2D (primary endpoint) defined as HbA1c≥6.5% or new physician diagnosis and on treatment.
2. Measure waist circumference, weight and a defined set of clinical, lifestyle, biochemical and outcome data (secondary endpoints).

In addition, a representative sample (expected ~5%) of South Asians screened but not meeting criteria for central obesity or prediabetes will be invited for reassessment to enable estimation of the sensitivity and specificity of waist circumference and HbA1c as screening tools for identification of South Asians at increased risk of T2D.

Organisation

Follow-up assessments will be at 12, 24 and 36 months after recruitment, and will be carried out by study research nurses (ie not the community health worker providing the intervention). Follow-up visits will take place in the same location as the intervention clinics, and using the same systems for providing appointments and appointment reminders. Appointments will last 30-60 minutes, and will be held in the morning. Index cases will be asked to attend in the fasting state (overnight) and accompanied by their consenting family members.

Follow-up assessment

At each follow-up visit we will complete a structured assessment that mirrors enrolment evaluation. This includes:

1. Follow-up questionnaire (**Appendix B**)
2. Physical measurements including waist circumference, weight and blood pressure.
4. Physical activity: Global Physical Activity Questionnaire (GPAQ)
5. Health-related quality of life states consisting of five dimensions Questionnaire (EQ-5D-5L)
6. Fasting venous blood sample (**Table 9.2**) for measurement of HbA1c and serum lipids

Protocols and equipment will be identical to those used for the baseline evaluation. Data will be entered onto the study database.

Assessment of the family members

Waist circumference, weight, waist-hip ratio and body mass index will be measured for the consenting family members. No blood tests.

Laboratory assays.

HbA1c assays will be run in the identified study laboratories (**section 9.1**)

9.4. Study drop-outs

Our power study design and power calculations allow for a 10% drop rate amongst index cases, a conservative estimate compared with published experience for intensive lifestyle modification in South Asians. Efforts will be made to contact all non-attenders, by telephone, home visits and contact with family members.

10. STATISTICS PROCEDURES

10.1. Sample size justification

The sample size calculations are based on the expected incidence of the primary outcome, new onset T2D, amongst study participants.

Based on prospective data amongst South Asians in the LOLIPOP study we expect the annual incidence of T2D in the control group to be

- South Asians with waist≥100cm 5.9%
- South Asians with HbA1c≥6.0% 14.6%
- Overall (waist≥100cm and / or HbA1c≥6.0%) 6.8%

Given the prevalence of risk factors observed in our population studies, we expect ~50% of our 3,600 participants to have HbA1c≥6.0% (ie 1,800), and ~75% to have waist≥100cm (ie ~2,700). With a sample size of 3,600 we therefore expect to identify up ~734 cases of new onset T2D over three years under the null hypothesis.

Power calculations to identify a reduction in the incidence of T2D for intensive lifestyle modification vs usual care (primary endpoint) under varying assumptions regarding recruitment, drop out and event rate are shown in **Tables 10.1** and **10.2**. Power remains good-high even in extreme situations. Assuming a 10% dropout rate, with a 1:1 allocation ratio, a total of 120 clusters each of size 30, our study has 80% power to identify at P<0.017, a reduction in the incidence of T2D for intensive lifestyle modification vs usual care (primary endpoint) of:

- South Asians with waist≥100cm 30%
- South Asians with HbA1c≥6.0% 24%
- Overall (waist≥100cm and / or HbA1c≥6.0%) 24%

Our study is thus well powered to detect the ~42% reduction in risk predicted from our studies of family-based intervention in the UK, and the effect sizes for reduction of risk of T2D observed in published studies of lifestyle modification vs usual care for prevention of T2D (30-60%, **section 4.3**).

Table 10.1: Reduction in risk of T2D for intensive lifestyle modification vs usual care detectable with 80% power, at P<0.017 under alternate assumptions. Baseline predicted event rates for usual care are: 5.9% in South Asians with waist≥100cm, 14.6% in South Asians with HbA1c≥6.0%, and 6.8% overall

Assumptions			**Risk reduction detectable in South Asians with**		
Sample size	**Event rate**	**Drop out rate**	**waist≥100cm**	**HbA1c≥6.0%**	**HbA1c ≥6.0% and / or waist≥100cm**
3,600	Baseline	10%	30%	24%	24%
3,600	**20% lower**	10%	32%	26%	27%
3,600	**40% lower**	10%	37%	30%	30%
3,600	Baseline	**20%**	31%	25%	26%
3,600	Baseline	**30%**	33%	27%	27%
3,000	Baseline	10%	32%	26%	26%
2,500	Baseline	10%	35%	29%	29%
2,500	**20% lower**	**20%**	38%	33%	33%

Table 10.2: Power to detect a 30% reduction in risk of T2D for intensive lifestyle modification vs usual care at P<0.017 under alternate assumptions. Baseline predicted event rates for usual care are: 5.9% in South Asians with waist≥100cm, 14.6% in South Asians with HbA1c≥6.0%, and 6.8% overall

Assumptions			**Risk reduction detectable in South Asians with**		
Sample size	**Event rate**	**Drop out rate**	**waist≥100cm**	**HbA1c≥6.0%**	**HbA1c ≥6.0% and / or waist≥100cm**
3,600	Baseline	10%	80%	95%	93%
3,600	**20% lower**	10%	71%	92%	88%
3,600	**40% lower**	10%	57%	80%	72%
3,600	Baseline	**20%**	76%	93%	90%
3,600	Baseline	**30%**	70%	90%	85%
3,000	Baseline	10%	74%	91%	90%
2,500	Baseline	10%	65%	85%	84%
2,500	**20% lower**	**20%**	48%	88%	49%

10.2. Randomisation

The clinical trial will compare intensive lifestyle intervention with usual care. This can only be done in an unblinded fashion (participant and provider). We will therefore use cluster randomisation of recruitment sites (rather than individual participant randomisation) to allocate treatment group. Cluster randomisation reduces the risk of resentful demoralisation and Hawthorne effect (contamination) during unblinded interventions.

In each of the 4 participating countries 50% of the recruitment sites will be randomly allocated to family based lifestyle modification (intervention) and 50% to usual care (control). Cluster randomisation will be carried out using random number generation and a simple algorithm implemented in a computer package. Randomisation will be done before recruitment commences.

10.3. Statistical analysis

Study endpoints

- Primary endpoint: new onset T2D in the index case defined as i. HbA1c≥6.5% or ii. Physician diagnosis and on medication for diabetes.

- Secondary endpoints in index cases will be:
  a. Physical: waist circumference, weight and blood pressure
  b. Lifestyle: cigarette and alcohol intake, physical activity
  c. Biochemical: Fasting glucose and lipids (Total and HDL cholesterol, Triglycerides)

- Secondary endpoints in family members: waist circumference and weight

Data Management and Analysis Committee

The Data Management and Analysis Committee will be responsible for the primary and secondary analyses of the study endpoints, and for preparing technical reports for dissemination of the research findings.

The Data Management and Analysis Committee will include: Chambers (Imperial), Jarvelin (Oulu), Stronks (AMC), Kooner (LNWHT), Wickremasinghe (UKEL), Jha (DDF) and Khadija (SIMS), supported by Post-doctoral statisticians with relevant expertise. The committee thus includes established expertise in analysis of data from clinical trials, population epidemiology, social and environmental epidemiology, life-course epidemiology and public health. All the investigators are highly experienced with the analysis of data from South Asian populations.

Data Management and Analysis plan:
All analyses will be carried out according to a Data Management and Analysis Plan prepared by the analysis team and agreed by the PIs.

Primary analyses will investigate whether intensive lifestyle modification reduces the risk of new onset T2D (primary endpoint) compared to usual care amongst South Asians with:

i. Central obesity [analysis of ~2,700 South Asian participants with waist≥100cm at recruitment]
ii. Prediabetes [analysis of ~1,800 South Asian participants with HbA1c≥6.0% at recruitment]
iii. Central obesity and / or prediabetes [combined analysis of all ~3,600 South Asian participants]

In each of these 3 groups the cumulative incidence of T2D will be compared between treatment arms (active versus control – intention to treat analysis) using random effects logistic regression to estimate odds ratios and 95% CI. The model will include randomisation stratum as a fixed effect and will adjust for clusters and other baseline measures including but not limited to age, gender, waist circumference and HbA1c. Statistical significance for the primary analyses will be inferred at $P<0.017$ to provide a conservative correction for the three hypotheses tested.

Risk reduction (absolute and relative) will be compared between the 3 groups. Cox proportional hazards regression will be applied to compare time to T2D onset between arms, with the same adjustments applied as in primary analysis.

Secondary analyses will include comparisons of intensive lifestyle modification for prevention of T2D between genders and other key population subgroups, and investigation of intensive lifestyle modification on secondary endpoints (the behavioural, psychosocial, clinical, and biochemical measures in index cases and family members).

Subgroup Analyses. Clinical effectiveness for T2D prevention will be examined in predetermined subgroups including gender, rural vs urban, and high vs low income region. Effectiveness will also be quantified according to baseline waist circumference and HbA1c to compare outcomes at differing thresholds for adiposity and abnormal glucose metabolism. The subgroup analyses will be conducted with a focus on the evidence for an interaction effect (difference in treatment effects in the two arms). Hence, subgroup-specific treatment effect estimates and p-values will be presented only if the interaction effect is statistically significant.

Methodological considerations
Blinding and Data handling. As the trial involves active intervention on both arms, it is not possible for participants and intervention staff to be blinded. However, outcome assessors and data analysts will be kept blind to the allocation. The trial aims to adhere to established procedures to maintain separation between staff that take outcome measurements and staff that deliver the intervention. Staff members who obtain outcome measurements will not be informed of the group assignment. Intervention staff and dieticians who deliver the intervention will not take outcome measurements during follow-up. All investigators, staff, and participants will be kept masked to outcome measurements and trial results.

Timing of Analyses. The final primary analysis will be performed 3 years from the data of recruitment for the last index case. Analysis of recruitment and intervention data will be conducted at month 16 and 27 respectively. An interim analysis of T2D incidence amongst controls will be carried out at 42 months.

Interim analyses. We will determine the incidence of T2D incidence in the control group at 2 years to assess whether T2D incidence is lower than anticipated (eg healthy cohort effect). Results will be presented to the work package lead used to reassess study power. If power falls substantially below 80% to identify a 25% reduction in the incidence of T2D with intervention, the other work package leads will be informed, and the implications and strategies for extending follow up and restore study power discussed. Other investigators, including field-workers, will not be informed of results from interim analysis to prevent potential bias in subsequent interactions with subject. Snapshots of the data used for interim analysis as well as analysis plans, programming code and reports will be preserved, allowing others to recreate the decision process from the trial archive if necessary.

Interim reports. Follow-up rates and data-quality reports will be generated monthly, stratified by region, country, location and gender, to enable deviation from expectations. Monthly reports will be distributed to the participant leads involved in the fieldwork, as well the project management team. Annual reports will summarise progress for the whole year and will be distributed to the consortium. Performance boundaries will be agreed and used to initiate strategic reviews and avoid deviation from the overall goal of complete follow-up in at least 90% of index cases.

Populations. All analysis will be performed with intention to treat on the full analysis population, defined as all participants who were randomised and participated in at least one post-baseline assessment.

Pooling of Data. The trial will be conducted under a common protocol for each centre with the intention of pooling the data for analysis. Every effort will be made to promote consistency in study execution at each investigational site. The consistency of the treatment outcome will be investigated across the centres to identify if there are extreme centres that could affect the interpretation of common statistical and clinical conclusions. A sensitivity analysis will be performed to identify potentially extreme centres.

Missing Data. In keeping with the intention-to-treat philosophy, the primary analysis will be done on all randomised participants who attended at least one post-baseline assessment. Participants who withdraw, are lost to follow-up, or have missing data will be included in the analysis. Missing data will be imputed using multiple imputation methods.

Treatment Compliance. Treatment compliance for the active arm will be estimated based on the number of times the index cases turn up for the weekly lifestyle modification sessions over the first 3 months period and subsequent monthly reinforcement sessions for 9 months.

Safety Analyses. The incidence of adverse events will be compared between the two arms. When calculating the incidence of adverse events, or any sub-classification such as time period or severity, each subject will only be counted once and any repetitions will be ignored, with the denominator being the total population size.

Data presentation. All continuous variables will be summarised using the following descriptive statistics: n (non-missing sample size), mean, standard deviation, median, maximum and minimum. The frequency and percentages (based on the non-missing sample size) of observed levels will be reported for all categorical measures. In general, all data will be listed, sorted by site (country), treatment arm and subject, and when appropriate by visit number within subject. All summary tables

will be structured with a column for each treatment in the order (Control, Experimental) and will be annotated with the total population size relevant to that table/treatment, including any missing observations.

Demographic and baseline variables. Demographic data including but not limited to age, ethnicity and gender, and baseline characteristic including but not limited to concurrent illnesses and medical conditions, as well as prior and concurrent medications will be recorded and summary statistics produced as described above. Comparisons between the active and control groups will be conducted to assess the degree to which comparability of randomisation was achieved.

Reporting Conventions. P-values ≥0.001 will be reported to 3 decimal places; p-values less than 0.001 will be reported as "<0.001". The mean, standard deviation, and any other statistics other than quantiles, will be reported to one decimal place greater than the original data. Quantiles, such as median, or minimum and maximum will use the same number of decimal places as the original data. Estimated parameters, not on the same scale as raw observations (e.g. regression coefficients) will be reported to 3 significant figures.

Technical Details. SPSS, Stata and R will be used for data analysis. To ensure reproducibility and accuracy, a second review statistician will independently reproduce the primary analyses and summary statistics tables. The reviewing statistician will have an overview of the entire analyses and will explicitly check the code producing summary tables selected at random as well as any other pieces of code as desired.

10.4 Health Economic analyses

Summary

The primary aim of the health economic analysis is to determine the cost-effectiveness of family based lifestyle modification vs usual care for prevention of T2D amongst i. South Asians on the Indian subcontinent and ii. South Asians in Europe. The health economic analyses will include pre-specified subgroup analyses including assessment of cost-effectiveness between:

1. South Asians identified to be at high risk of T2D based on i. central obesity (waist≥100cm) vs ii. Prediabetes (HbA1c≥6.0%)
2. Low-middle-income (Indian subcontinent) vs high-income (UK) regions
3. Men and women, socioeconomic classes, and across ages
4. Participating countries: India, Pakistan, Sri Lanka and the UK.

These estimates will enable assessment of the scalability of family based lifestyle intervention to prevent T2D amongst South Asians with centrally obesity and/or prediabetes, and the potential clinical and financial implications of implementing the approaches into standard practice.

Data collection to enable health economic evaluation.

During the RCT, participants will complete validated questionnaires to record health care resource use, health care expenses and time away from employment due to ill health. The study Health Economic research assistants (RAs) will be responsible for data collection to validate information on the local costs for relevant health care activities, or collating this where it does not exist. The cost analysis will impute generalizable costs of delivery in the public sector having updated information from previously published studies in India and Sri Lanka, and will undertake a rapid assessment to estimate similar costs for Pakistan

Methods for health economic evaluation

A full health economic analysis will be undertaken to assess the cost-effectiveness of intensive lifestyle modification versus usual care. The primary measures of effectiveness will the incremental cost per case of diabetes avoided and per quality-adjusted life years (QALYs), and net monetary

benefit for the health system including patients at three years post intervention. The primary analysis will be carried out for the Indian subcontinent and Europe separately. Cost-effectiveness at three years will be determined using the resource utilisation and outcome data collected during the cluster-RCT. We will estimate the average cost per participant in each arm of the trial, including cost of setting up, delivering and maintaining the intervention. The cost analysis will also take a health and personal health services perspective. Quality of life data from the EQ5D will be combined with survival data using linear interpolation to report QALYs at three years. We will report the mean (95% confidence interval) incremental costs and we will use multilevel linear regression models to allow for clustering. Analyses will adjust for pre-specified baseline covariates at both patient and site level.

Predicted survival and quality of life data will be combined to report lifetime QALYs, and to project lifetime incremental costs, incremental QALYs, and incremental net benefits for the alternative strategies of care. Long-term modelling will extrapolate from the cluster randomized trial (CRT) data by fitting alternative parametric survival curves (e.g. Weibull, exponential, lognormal, log logistic and Gompertz) to the observed survival data. The chosen method of extrapolation for the base case will be the one judged most plausible. In the base case, quality of life calculated at three years will be assumed to apply to each subsequent year of life, after allowing for decrements in quality of life according to advancing age. Sensitivity analyses will test whether the results are robust to methodological assumptions (e.g. specification of the statistical model, extrapolation approach, alternative quality of life assumptions, and learning curve effects). Planned subgroup analyses will compare cost-effectiveness between the two screening strategies (waist vs HbA1c), and between gender, socioeconomic classes and geographic regions.

The results of the cost-effectiveness analyses will be used to describe the potential implications (benefits and costs) in the local and national health economies of scaling-up intensive lifestyle modification for prevention of T2D, using central obesity and / or HbA1c for screening, taking account of gender, and in different environmental settings. The analyses of the costs of scaling-up will take into account available and future resource envelopes in the South Asian countries, and also current and future pricing for assays such as HbA1c, to understand current and future feasibility.

11. DATA MANAGEMENT

11.1. Source Documents and Data

Source document
All original documents, data and records from which participant data is obtained will be considered a source document. This includes documents such as:
- Hospital records
- Laboratory and pharmacy records
- Diaries
- Microfiches
- GP's opinion of eligibility
- Correspondence

Source Data
All information contained in source documents will be considered source data.

Direct access to source documents containing patient's identifiable details should be granted to non-medical staff for the purposes of research, monitoring, audit and regulatory inspection. Non-medical individuals and parties who will be expected to have access to source documents are:

- Research team
- Regulatory authorities
- Authorised representatives of the Sponsor
- Authorised representative of relevant NHS or relevant host organisation

11.2. Language
All written material to be used by subjects will be translated in the local languages and will use vocabulary that is clearly understood. Generic names for concomitant medications will be recorded in the CRF wherever possible.

11.3. Database
The quantitative research data comprising anonymised clinical questionnaires, physical measurements, and biochemical data will be stored on a customised InForm database, held on a secure encrypted server at Imperial College London. InForm is a web-based data entry system based on the Oracle database platform. InForm is the established tool for clinical trials at Imperial College, and incorporates an inbuilt reporting package, Cognos.

Data will be stored in full compliance with relevant national legislation, and with international guidance on best practice. Data will be held on the server in a linked anonymised format (personal identifiers removed). User-level permissions will regulate access to data. Linked anonymised data will be available to statisticians, research assistants and work package leads. Fully anonymised data will be available to all partners.

The InForm team provides Clinical Trial Teams across ICL with support for collection, management and analysis of data from clinical trials. InForm designs and builds the electronic case report forms (eCRFs) and validation rules for data entry to ensure the data can be collected accurately and stored securely. The InForm team provides support during the life cycle of the trial and assistance with *ad hoc* report development, and provides research data extracts for safety committees, final reports and others.

11.4. Data collection and record keeping

Data will be collected in paper copy and transposed in a linked anonymised fashion to InForm. Subject files and other source data (including copies of protocols, CRFs, original reports of test results, correspondence, records of informed consent, and other documents pertaining to the conduct of the study) will be retained and stored in locked filing cabinets in a locked room, in a secure part of the respective partner organisation. Only the local PI and approved researchers will have access to the store. The paper copies will be backed up to an image archive at each partner organisation, stored on a secure server with user-level security and regular back-up. The paper copies and image files will be held for 10 years after the research is complete (or longer if national regulations require). Thereafter the paper and electronic file will be “shredded” using appropriate secure, validated technology. Personal identifiable information will not be shared between sites. Qualitative data collected during focus groups will be stored locally, with anonymised transcripts and summaries shared with the consortium through the study database.

No study document will be destroyed without prior written agreement between the Sponsor and the investigator. Should the investigator wish to assign the study records to another party or move them to another location, written agreement will obtained from the Sponsor.

12. REGULATORY ISSUES

12.1. Research Ethics approval

This study will not open to recruitment until appropriate approvals and authorisations have been obtained from an independent ethical committee. In the same way, recruitment will not commence at an individual participating site until local NHS Management approval has been obtained and all local documentation is in place and all requirements have been fulfilled according to this project's Standard Operating Procedures (SOPs). The Chief Investigator will require a copy of site specific R&D approval letters before accepting participants into the study. The study will be conducted in accordance with the recommendations for physicians involved in research on human subjects adopted by the 18th World Medical Assembly, Helsinki 1964 and later revisions.

12.2. Consent

Consent to enter the study will be sought from each participant only after a full explanation has been given, an information leaflet offered and time allowed for consideration. Signed participant consent will be obtained. The right of the participant to refuse to participate without giving reasons will be respected. After the participant has entered the study the clinician remains free to give alternative treatment to that specified in the protocol at any stage if he/she feels it is in the participant's best interest, but the reasons for doing so will be recorded. In these cases, the participants remain within the study for the purposes of follow-up and data analysis. All participants are free to withdraw at any time from the protocol treatment without giving reasons and without prejudicing further treatment.

12.3. Confidentiality

The Chief Investigator will preserve the confidentiality of participants taking part in the study and is registered under the Data Protection Act. The investigators will ensure that the subject's confidentiality is maintained. On the CRF or other documents submitted to the Sponsors, subjects will be identified by a subject ID number only. Documents that are not submitted to the Sponsor (e.g., signed informed consent form) will be kept in a strictly confidential file by the investigators. Investigators will only permit direct access to subjects' records and source document for the purposes of monitoring, auditing, or inspection by the Sponsor, authorised representatives of the Sponsor and RECs.

12.4. Indemnity

Imperial College London holds negligent harm and non-negligent harm insurance policies which apply to this study.

12.5. Sponsor

Imperial College London will act as the main Sponsor for this study. Delegated responsibilities will be assigned to the NHS trusts taking part in this study. Each partner institution involved in the recruitment of patients will have their own Sponsor.

12.6. Funding and financial aspects

The research is funded by the European Commission (Grant award 643774: €3,614,083.75 for January 2015 to December 2019). There are no financial conflicts of interest.

12.7. Audits and inspections

The study may be subject to inspection and audit by Imperial College London under their remit as sponsor and other regulatory bodies to ensure adherence to GCP and the NHS Research Governance Framework for Health and Social Care (2nd edition).

13. STUDY MANAGEMENT

The iHealth-T2D project involves partners from two continents: Europe and the Indian subcontinent. The management structure has been designed to take into account the global nature of the project, and to balance the competing priorities of international collaboration with the needs for robust reporting and project delivery.

13.1 Partner organisations

The participating organisations and their lead investigators are summarised in **Table 13.1**. The lead investigators will be the primary contact for the respective organisation, and will work closely with the trial team to ensure that the research project is completed to time and to target. There will be an annual face-face meeting with all partners, supplemented by email and teleconference contact as required.

Table 13.1. Lead investigators at participating organisations.

Partner no	Participating organisation	Short name	Lead investigator
1	Imperial College London	Imperial	Dr John Chambers
2	Devki Devi Foundation	DDF	Dr Sujeet Jha
3	University of Colombo	UCOL	Dr Prasad Katalunda
4	University of Kelaniya	UKEL	Prof Raj Wickremasinghe
5	University of Surrey	SURREY	Prof Graham Cookson
6	London North West Healthcare NHS Trust	LNWH	Prof Jaspal S Kooner
7	Institute of Health Policy	IHP	Dr Ravindra Rannan-Eliya
8	University of Amsterdam	AMC	Dr Karien Stronks
9	University of Oulu	OULU	Prof MR Jarvelin
10	Punjab Institute of Cardiology	PIC	Dr Sajjad Ahmed
11	Services Institute of Medical Sciences	SIMS	Dr KI Khawaja

13.2. Trial Steering Committee

The Trial Steering Committee will provide overall supervision of trial conduct and progress, and will review and approve any changes needed to the study protocol. The Trial Steering Committee will comprise: i. the Chief Investigator (Chambers, Imperial, Chair) and lead investigator from each of the participating organisations (**Table 13.1**), and ii. two patient representatives (one from Europe, one from South Asia, both **TBA**), The Trial steering committee will meet every 12 months, supplemented by teleconference every 3 months, and email contact as required.

13.3. Data Monitoring and Analysis Committee

A Data Monitoring and Analysis Committee will be established to assure maintenance of the trial database system, data collection, entry, verification and analysis. This Committee will also overlook ethical issues, patient safety and proper conduct of the trial. The composition of the Data Monitoring and Analysis Committee is summarised in **Table 13.2**. and includes two members from organisations not participating in recruitment or intervention, and thus independent of the main research effort (**OULU** and **AMC**), a chair independent from the Project Management Team (**Professor JS Kooner, LNWHT**), one lead investigator from each country involved in data

collection, one statistician, and the Chief Investigator. This Committee will be meet every 6 months, supplemented by teleconference and email as required.

Table 13.2. Data Monitoring and Ethical Committee

Position	Name	Institution
Chair	Professor J Kooner	LNWHT, UK
Member	Professor MR Jarvelin	Oulu, Finland
Member	Professor K Stronks	AMC, Netherlands
Member	Dr Sujeet Jha	DDF, India
Member	Dr K Khawaja	SIMS, Pakistan
Member	Dr R Wickremasinghe	UKEL, Sri Lanka
Member	Prof J Chambers	Imperial, UK
Statistician	To be appointed	TBC

13.4 Project Management Team

Day-to-day management of the study will be co-ordinated through the project's management team, based at Imperial College London. The Project Management Team will be responsible for day-day administrative and scientific management of the project, including study planning, organisation of meetings, delivery of the annual risk report, responsibility for the trial master files and compliance with all necessary reviews.

The management team will be led by the Chief Investigator Professor John Chambers, Imperial College London, and will comprise:

i. Project Coordinators with established expertise in administration management of projects, grants and awards from a variety of funding bodies
ii. Clinical Trial Coordinators with established expertise in scientific management, including the design and conduct of clinical trials
iii. Data controller to manage the study website and research data generated.

The Project Management Team will be based in the Department of Epidemiology and Biostatistics at Imperial College London (Imperial). Recognising the global nature of the research, which will require extensive fieldwork by multiple partners across India, Pakistan and Sri Lanka, the Project Management Team will include a Regional Project Coordinator (based at DDF, India) and four Regional Clinical Trial Coordinators (two each based in Pakistan and Sri Lanka) and working jointly with their counterparts based at Imperial. The Project Management Team will work closely with Principal Investigators at the participating organisations to deliver both Administrative and Scientific Project Management.

Table 13.3. Project Management Team

Position	Name	Institution
Chair	Prof J Chambers	Imperial
Project Manager	Ms Ninha Silva	Imperial
Regional Project Manager	Mr Rajesh Saxena	DDF
Regional Clinical Trial Coordinator	Dr Khurram Shahzad	PIC
Regional Clinical Trial Coordinator	Dr Sara Mahmood	SIMS
Regional Clinical Trial Coordinator	Ms Achini Weerasinghe	UCOL
Regional Clinical Trial Coordinator	Dr Anuradhani Kasturiratne	UKEL
Data Controller	Dr Benjamin Lehne	Imperial

The Project Management Team will be responsible for the following tasks:

Research ethics. Obtaining Institutional Review Board approval for the study in each country, and at each research location. Ensuring information sheets and consent forms are translated into the major South Asian languages. Creating short videos that describe the project in key South Asian languages, to facilitate obtaining consent. Public registration of the Clinical Trial (eg ClinicalTrials.gov). Working to ensure the research is carried out using good clinical practice (GCP), ethically (Declaration of Helsinki) and rigorously (International Conference on Harmonization Guidelines). Providing annual reports to Institutional Review Boards.

Co-ordinate and manage the clinical trial. Collating study materials from the partners, and ensuring they are consistent with study protocol. Maintaining the study master file to ensure that all aspects of the research are properly documented, and allow accurate reporting, interpretation and verification. Monitor and report on subject recruitment, compliance with study protocols across sites, and data quality. Manage adverse event recording and reporting. Be responsible for study close-out, including working with the partners in completing outstanding findings and queries. Ensure compliance with local, national and international record retention policies.

Development of Study database. The Project Management Team will establish a customised database for: collection, management and storage of the study research data; recording details of study personnel involved with the study and their roles; and for data and quality assurance including complete audit trail. The database will be held on a secure encrypted server, managed day-day by the study Data controller and with user-level permissions will regulate access to data. Participant identifiable information will only be available to the principal investigator at the respective research location.

Organise Trial Steering Committee meetings There will be annual face-face meetings. Reflecting the major role of South Asian partners, meetings will be held in Europe and South Asia. Meetings will be attended by all the Principal Investigators. The purpose of these meeting is to ensure that all members are aware of their obligations, and are in a position to meet their agreed deliverables. Meetings will review the progress of the project to date, including interpretation of the research results, identify potential risks and problems, and agree strategy for future implementation.

Project Website and Dissemination activities. A project web-site has been created to promote the project (www.ihealth-t2d.eu). Support the partners in disseminating and exploiting the results of the research, through public, clinical, scientific and policy meetings. Assisting with scheduling, preparation and printing of materials, and providing a contact point for the public, press and other experts.

14. PUBLICATION POLICY

During the project, data and knowledge will be managed through the study Data Access and Publications committee. This will comprise the Project lead (chair), the Principal Investigators from each participating organisation, and other partner representatives at the direction of the committee. Two external, independent scientists will be invited to join the data access and publications committee to ensure the principles and practice of data and knowledge management are followed.

In keeping with the principles for publication and access to clinical trial data recently proposed by the EMA (2013) and other international regulatory bodies, a fully anonymised copy of the research data will be made available for use by other investigators at the end of the research. This will allow transparency and public scrutiny, and secondary use of the data. Before data release, effective measures will be implemented to prevent participant identification through data mining.

15. REFERENCES

1. Knowler WC, Barrett-Connor E, Fowler SE, et al. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. The New England journal of medicine 2002;346:393-403.
2. Ramachandran A, Snehalatha C, Mary S, et al. The Indian Diabetes Prevention Programme shows that lifestyle modification and metformin prevent type 2 diabetes in Asian Indian subjects with impaired glucose tolerance (IDPP-1). Diabetologia 2006;49:289-97.
3. Group AC, Patel A, MacMahon S, et al. Intensive blood glucose control and vascular outcomes in patients with type 2 diabetes. The New England journal of medicine 2008;358:2560-72.
4. Shaw JE, Sicree RA, Zimmet PZ. Global estimates of the prevalence of diabetes for 2010 and 2030. Diabetes research and clinical practice 2010;87:4-14.
5. Ebrahim S, Kinra S, Bowen L, et al. The effect of rural-to-urban migration on obesity and diabetes in India: a cross-sectional study. PLoS medicine 2010;7:e1000268.
6. McKeigue PM, Shah B, Marmot MG. Relation of central obesity and insulin resistance with high diabetes prevalence and cardiovascular risk in South Asians. Lancet 1991;337:382-6.
7. Ramachandran A, Ramachandran S, Snehalatha C, et al. Increasing expenditure on health care incurred by diabetic subjects in a developing country: a study from India. Diabetes care 2007;30:252-6.
8. Tuomilehto J, Lindstrom J, Eriksson JG, et al. Prevention of type 2 diabetes mellitus by changes in lifestyle among subjects with impaired glucose tolerance. The New England journal of medicine 2001;344:1343-50.
9. Ramachandran A, Snehalatha C, Yamuna A, Mary S, Ping Z. Cost-effectiveness of the interventions in the primary prevention of diabetes among Asian Indians: within-trial results of the Indian Diabetes Prevention Programme (IDPP). Diabetes care 2007;30:2548-52.
10. Weber MB, Ranjani H, Meyers GC, Mohan V, Narayan KM. A model of translational research for diabetes prevention in low and middle-income countries: The Diabetes Community Lifestyle Improvement Program (D-CLIP) trial. Primary care diabetes 2012;6:3-9.
11. Sathish T, Williams ED, Pasricha N, et al. Cluster randomised controlled trial of a peer-led lifestyle intervention program: study protocol for the Kerala diabetes prevention program. BMC public health 2013;13:1035.
12. DS10-A5: A translational randomized trial of culturally specific and cost-effective life style intervention for the prevention of type 2 diabetes in Pakistan (Pakistan Diabetes Prevention Program PDPP). 2014, at http://www.idf.org/bridges/d-start/DS10-A5.)
13. Ramachandran A, Snehalatha C, Ram J, et al. Effectiveness of mobile phone messaging in prevention of type 2 diabetes by lifestyle modification in men in India: a prospective, parallel-group, randomised controlled trial. The lancet Diabetes & endocrinology 2013;1:191-8.
14. Chambers JC, Elliott P, Zabaneh D, et al. Common genetic variation near MC4R is associated with waist circumference and insulin resistance. Nature genetics 2008;40:716-8.
15. Chambers JC, Zhang W, Zabaneh D, et al. Common genetic variation near melatonin receptor MTNR1B contributes to raised plasma glucose and increased risk of type 2 diabetes among Indian Asians and European Caucasians. Diabetes 2009;58:2703-8.
16. Kooner JS, Chambers JC, Aguilar-Salinas CA, et al. Genome-wide scan identifies variation in MLXIPL associated with plasma triglycerides. Nature genetics 2008;40:149-51.
17. Bonora E, Tuomilehto J. The pros and cons of diagnosing diabetes with A1C. Diabetes care 2011;34 Suppl 2:S184-90.
18. Ramachandran A, Mary S, Yamuna A, Murugesan N, Snehalatha C. High prevalence of diabetes and cardiovascular risk factors associated with urbanization in India. Diabetes care 2008;31:893-8.
19. Skar M, Villumsen AB, Christensen DL, et al. Increased risk of type 2 diabetes with ascending social class in urban South Indians is explained by obesity: The Chennai urban rural epidemiology study (CURES-116). Indian journal of endocrinology and metabolism 2013;17:1084-9.
20. Houselisting and Housing Census Data Highlights - 2011: Census of India.

21. Bhopal RS, Douglas A, Wallia S, et al. Effect of a lifestyle intervention on weight change in south Asian individuals in the UK at high risk of type 2 diabetes: a family-cluster randomised controlled trial. The lancet Diabetes & endocrinology 2014;2:218-27.
22. Admiraal WM, Vlaar EM, Nierkens V, et al. Intensive lifestyle intervention in general practice to prevent type 2 diabetes among 18 to 60-year-old South Asians: 1-year effects on the weight status and metabolic profile of participants in a randomized controlled trial. PloS one 2013;8:e68605.
23. Chapman J, Qureshi N, Kai J. Effectiveness of physical activity and dietary interventions in South Asian populations: a systematic review. The British journal of general practice : the journal of the Royal College of General Practitioners 2013;63:e104-14.
24. Chan JC, Malik V, Jia W, et al. Diabetes in Asia: epidemiology, risk factors, and pathophysiology. JAMA : the journal of the American Medical Association 2009;301:2129-40.
25. Deepa M, Anjana RM, Manjula D, Narayan KM, Mohan V. Convergence of prevalence rates of diabetes and cardiometabolic risk factors in middle and low income groups in urban India: 10-year follow-up of the Chennai Urban Population Study. Journal of diabetes science and technology 2011;5:918-27.
26. Misra A, Pandey RM, Devi JR, Sharma R, Vikram NK, Khanna N. High prevalence of diabetes, obesity and dyslipidaemia in urban slum population in northern India. International journal of obesity and related metabolic disorders : journal of the International Association for the Study of Obesity 2001;25:1722-9.
27. Diabetes in the UK 2010: Key statistics on diabetes - Minority Report: Diabetes UK.