CLINICAL STUDY PROTOCOL

Protocol Title

Performance and usability evaluation of cardiometabolic point-of-care devices in a target use setting

Short title

Cardiometabolic devices study

Protocol Version Number:

NC001 v2.0

Date:

30-March-2022

Disease Programme:

Non-communicable diseases (NCDs)

Regulatory Agency Identifying Number(s):

NHRC Proposal ID: 654/2021

Clinicalstudys.gov Registration Number:

NCT05257564

FIND
Campus Biotech
Chemin des Mines 9
1202 Geneva, Switzerland
T: +41 (0)22 710 05 90

Confidentiality Statement:

FIND
Diagnosis for all

Table of Contents

Institutions/Organizations/Partners Involved in the Study **6**
Signature Page (Sponsor) **7**
Statement of Principal Investigator **8**
Protocol History/Amendment Summary* **9**
List of Abbreviations and Acronyms **10**
Protocol Synopsis **11**
Schedule of Activities **12**
1 Introduction **13**
1.1 Study Rationale 13
1.2 Background 14
1.3 Benefit/Risk Assessment 14
2 Study Objectives and Endpoints **14**
3 Study Design **15**
3.1 General Design 15
3.2 Scientific Rationale for Study Design 16
3.3 End of Study Definition 16
3.4 Study Population and Eligibility 16
3.5 Inclusion Criteria 17
3.6 Exclusion Criteria 17
3.7 Lifestyle Considerations 17
3.8 Screen Failures 17
4 Study Intervention **17**
4.1 Investigational Product (or Study Intervention) 18
4.2 Preparation/Handling/Storage/Accountability 20
4.3 Minimisation of Error and Bias 21
4.3.1 Blinding Procedure 21
5 Participant Discontinuation/Withdrawal **21**
5.1 Participant Discontinuation/Withdrawal from the Study 21
6 Study Procedures **22**
6.1 Participant enrolment 24
6.2 Specimen Collection, Handling, Transport and Storage 24
6.2.1 Capillary blood sample collection 25
6.2.2 Venous blood sample collection 25

6.3 Index Test and Reference Test Procedures 25
6.3.1 Index tests procedure summary 25
6.3.2 Reference tests 26
6.4 Training 26
6.5 Genetic Analysis 26
6.6 Experimental Biomarkers 26
6.7 Other Tests (Specify) 27
6.8 Safety Assessments 27
6.9 Other Study Procedures 27
7 Safety and Incident Reporting 27
7.1 Medical Device Incidents (including Malfunctions) 27
7.2 Time Period for Detecting Medical Device Incidents 28
7.3 Follow-up of Medical Device Incidents 28
7.4 Reporting of Medical Device Incidents to FIND 28
7.5 Regulatory Reporting Requirements for Medical Device Incidents 28
8 Statistical Considerations 29
8.1 Populations for Analyses 29
8.2 Statistical Analyses 29
8.2.1 Analysis of primary and secondary outcomes 29
8.2.2 Safety Analysis 30
8.2.3 Other Analyses 30
8.3 Planned Interim Analyses 30
8.3.1 Data Monitoring Committee (DMC) 30
8.4 Sample Size Determination 31
8.5 Statistical software 31
9 Regulatory and Ethical Considerations 32
9.1 Regulatory and Ethics Approvals 32
9.2 Financial Disclosure 33
9.3 Informed Consent Process 33
9.4 Data Protection 33
10 Data Handling and Record Keeping 34
10.1 Source Data and Source Documents 34
10.2 Data Management 35
11 Quality Management 35

11.1 Quality Control (monitoring) 36
11.2 Quality Assurance (auditing) 36
11.3 Study and Site Closure 36
12 Publication Policy 36
13 References 37
14 Appendices 37
Appendix 1: Safety Definitions and Reporting 37
Appendix 2: Incident Definition and Reporting 39
Appendix 3: Protocol Amendment Summary Table 40

Institutions/Organizations/Partners Involved in the Study

Organization/Institution/Company/Partner	Role in the Study
FIND, Geneva, Switzerland	Sponsor
BP Koirala Institute of Health Science, Dharan, Nepal	Local institution for study implementation; principal investigator site
Hôpitaux Universitaires de Genève, Switzerland	Study manager and Sub-principal investigator site
Kakarvitta Health Post, Nepal	Investigational Site 1
Dhulabari Primary Healthcare Centre, Nepal	Investigational Site 2
B.P Koirala Institute of Health Sciences, Postal Code 56700, Ghopa Camp, Dharan, Province No.1, Nepal	Reference testing site
Tascom Ltd, South Korea	Device manufacturer
Jana Care, India/Boston	Device manufacturer

FIND (Sponsor)

Contact person: Dr. Beatrice Vetter
Address: Campus Biotech
Chemin des Mines 9
1202 Geneva, Switzerland

Nepal

Principal investigator: Dr. Sanjib Kumar Sharma

Sub-Principal investigator: Dr. Vijay Kumar Khanal
Dr. Sagar Poudel

Address: B.P. Koirala Institute of Health Sciences
Buddha Road, Dharan 56700, Nepal

Hôpitaux Universitaires de Genève (HUG)

Study Manager: Mrs. Marina Giachino

Sub-Principal Investigators: Dr. Jorge César Correia, Prof. Dr. med. Zoltan Pataky, Dr. Sigiriya Aebischer Perone, Mr. Bruno Lab, Mrs. Olivia Heller

Address: Unit of Therapeutic Patient Education; WHO Collaborating Centre
Division of Endocrinology, Diabetology, Nutrition and Therapeutic Patient Education; Department of Medicine
Geneva University Hospitals
Villa Soleillane; 7, Chemin Venel
1206 Geneva, Switzerland

Division of Tropical and Humanitarian Medicine
Geneva University Hospitals
Rue Gabrielle-Perret-Gentil 4
1205 Geneva, Switzerland

Terms of references and nature of agreements are available from FIND on request.

Signature Page (Sponsor)

We, the undersigned, have developed, reviewed and approved this protocol, including appendices. We will supervise and coordinate the clinical study according to the principles outlined in the Declaration of Helsinki and Good Clinical Practice and in compliance with applicable regulatory requirements.

DIRECTOR OF NCD PROGRAMME

Name:

Signature: _____ Digitally signed by Beatrice Vetter DN: cn=Beatrice Vetter, o, ou, email=beatrice.vetter@finddx.org, c=CH Date: 2022.04.25 21:34:11 +02'00' Date: _____

DD/MMM/YYYY

SENIOR MANAGER CLINICAL AFFAIRS

Name: Pamela Nabeta pp. Rita Szekely

Signature: _____ Date: 28/APR/2022

DD/MMM/YYYY

STUDY MANAGER

Name: Marina Giachino

Signature: _____ Date: 25/APR/2022

DD/MMM/YYYY

DIRECTOR, DATA SCIENCE

Name: Stefano Ongarello

Signature: _____ Date: 26/APR/2022

DD/MMM/YYYY

PRINCIPAL DATA SCIENTIST

Name: Aurélien Macé

Signature: _____ Date: 25/APR/2022

DD/MMM/YYYY

FIND
Diagnosis for all

Statement of Principal Investigator

In signing this page, I, the undersigned, agree to conduct the study according to the protocol and ICH-GCP E6 (R2) guidelines and in compliance with applicable regulations.

I will ensure that the requirements relating to obtaining Institutional Review Board (IRB)/ Independent Ethics Committee (IEC) review and approval are met. I will promptly report to the IRB/IEC any and all changes in the research activities covered by this protocol.

I have sufficient time to properly conduct and complete the study within the agreed study period and I have adequate resources (staff and facilities) for the foreseen duration of the study.

I am responsible for supervising any individual or party to whom I delegate study related duties and functions conducted at the study site. Further, I will ensure this individual or party is qualified to perform those study-related duties and functions.

I certify that key individuals involved with the conduct of this study, including myself, have completed GCP training and, if applicable, Human Subjects Protection Training.

I understand that all information obtained during the conduct of the study with regard to the subjects' state of health will be regarded as confidential. No participant's names or personal identifying information may be disclosed. All participant data will be anonymized and identified by assigned numbers on all Case Report Forms, laboratory samples and other study related information (such as essential documents) forwarded to FIND. Monitoring and auditing by FIND, and inspection by the appropriate regulatory authority(ies) (RA), will be permitted.

I will maintain confidentiality of this protocol and all other related investigational materials. Information taken from the study protocol may not be disseminated or discussed with a third party without the express consent of FIND.

Name of Principal Investigator: Prof. Dr. Sanjib Kumar Sharma
(Print)

Name:
Signature: _____ Date: 28/APR/2022
DD/MMM/YYYY

FIND
Diagnosis for all

Protocol History/Amendment Summary*

Version number	Release date	Comments
1.0		Initial version
2.0	30-MAR-2022	After Site Initiation Visit, Technical Amendments

*Refer to Appendices for Protocol Amendment History

FIND
Diagnosis for all

List of Abbreviations and Acronyms

Abbreviation/acronym	Meaning
CRF	Case Report Form
CVD	Cardiovascular Disease
EDL	Essential Diagnostic List
GCLP	Good Clinical Laboratory Practice
GCP	Good Clinical Practice
HbA1c	Glycated Haemoglobin
Hb	Haemoglobin
HUG	Hôpitaux Universitaires de Genève
ICF	Informed Consent Form
ICH	International Council on Harmonisation
IEC	Independent Ethics Committee
IFU	Instructions for Use
IRB	Institutional Review Board
ISF	Investigator Site File
KHDC	Chronic Kidney Diseases, Hypertension, Diabetes and Cardiovascular disease in Community
LMIC	Low and Middle Income Country
NCD	Non-communicable Disease
PEN	Package of Essential Non-communicable Diseases
POC	Point-of-Care
QA	Quality Assurance
QC	Quality Control
QMS	Quality Management System
PHC	Primary Healthcare
RA	Regulatory Authority
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SUS	System Usability Score
TPP	Target Product Profile
WHO	World Health Organisation

FIND
Diagnosis for all

Protocol Synopsis

Title	Performance and usability evaluation of cardiometabolic point-of-care devices in a target use setting
Short title	Cardiometabolic devices study
Version and date	V2.0 30-March-2022
Background and rationale	With the rise of cardiovascular diseases (CVD) and diabetes, the global disease burden is shifting towards non-communicable diseases (NCDs). An increasing number of low- and middle-income countries (LMICs) are currently experiencing the double burden of infectious and non-communicable diseases. In order to facilitate a patient-centred approach to healthcare, there is an urgent need to ensure that primary healthcare (PHC) facilities in LMICs are capable of addressing diagnosis and monitoring of non-communicable diseases at the point-of-care (POC). Important minimum parameters for PHC POC diagnosis and monitoring of cardiometabolic diseases are lipids/lipoproteins, glucose, glycated haemoglobin (HbA1c) and serum creatinine, to address cardiovascular disease, diabetes and chronic kidney disease. While several technologies of multi-parameter POC devices capable of supporting diagnosis and monitoring of cardiometabolic diseases exist, their quantitative accuracy is often not well evaluated outside of the manufacturer's laboratories and published independent evaluations can be rare, particularly in the settings of intended use. These settings are PHC facilities in varying climatic environments and with staff without specialist laboratory training. Our study aims to evaluate the quantitative accuracy of 2 cardiometabolic POC devices (the SimplexTAS 101 from Tascom and the Aina Station from JanaCare) in a setting of intended use and performed by the intended user.
Primary objective(s)	1.1. To determine the accuracy of quantitative measurements of glucose, HbA1c, total cholesterol and creatinine as measured in a healthcare setting with point-of-care multiparameter devices compared to a laboratory reference method
Secondary objective(s)	2.1 To evaluate the operational characteristics and system usability of each cardiometabolic device when used in a PHC setting
Primary endpoints (outcomes)	1.1. Estimates of correlation and linear dependence between quantitative measurements of glucose, HbA1c, total cholesterol and creatinine evaluated in a healthcare setting with point-of-care multiparameter devices and in a laboratory reference assay. 1.2. Estimates of accuracy and limits of agreement for quantitative measurements of glucose, HbA1c, total cholesterol and creatinine evaluated in a healthcare setting with point-of-care multiparameter devices (compared to a laboratory reference assay).
Secondary endpoints (outcomes)	2.1 Operational characteristics and usability of study devices: - Rate of invalid test results and error types - System usability score
Study design	Prospective quantitative accuracy study
Study sites/setting	Multi-centre: Dhulabari Primary Healthcare Centre, Kakarvitta Health Post, Nepal
Study population	Members of the local community attending the facility under the KHDC program
Sample Size	400
Eligibility criteria	Age: ≥20 years; KHDC clinic attendees; Hb ≥8 g/dL; Consenting
Study duration	4 months
Time schedule	Anticipated start Q1 2022

Schedule of Activities

Procedure	Daily (working days)	Weekly	Notes
Eligibility assessment	X		excluding haemoglobin testing
Informed consent	X		-
Haemoglobin testing	X		-
Demographic information	X		-
Fingerstick testing	X		-
Venous sample collection	X		-
Venous sample transport to reference lab	X		-
Reference lab testing	X		-
Data entry		X	-

1 Introduction

With the rise of cardiovascular diseases (CVD) and diabetes, the global disease burden is shifting towards non-communicable diseases (NCDs). An increasing number of low- and middle-income countries (LMICs) are currently experiencing the double burden of infectious and non-communicable diseases [1]. CVD and diabetes alone make up more than two thirds of the global burden of the four most common NCDs, including chronic respiratory diseases and cancer [2]. In order to facilitate a patient-centred approach to healthcare, there is an urgent need to ensure that primary healthcare (PHC) facilities in LMICs are capable of addressing diagnosis and monitoring of both infectious and non-communicable diseases at the point-of-care.

In 2020 the Foundation for Innovative New Diagnostics (FIND), together with technical inputs from the World Health Organization (WHO), developed a landscape of multi-parameter point-of-care (POC) devices capable of supporting diagnosis and monitoring of cardiometabolic diseases at PHC facilities [3]. Cardiometabolic risk factors include raised blood pressure, raised blood glucose, raised blood lipids, excess weight and obesity. The WHO Package of Essential Noncommunicable Disease Interventions for primary health care in low resource settings (WHO PEN package, [4], as well as the WHO Model List of Essential In Vitro Diagnostics (EDL, [5]), include several parameters for the use at POC that should be used to detect and manage cardiometabolic risk. These include lipids/lipoproteins, glucose, glycated haemoglobin (HbA1c) and serum creatinine, to address cardiovascular disease, diabetes and chronic kidney disease.

Together with a range of clinical and laboratory experts, FIND developed a target product profile (TPP) for cardiometabolic POC devices, with the aim to define the minimal and optimal requirements for such devices in PHC settings in LMICs [6]. Beyond the test menu available, requirements considered related to device design, usability, storage and operating temperature, data management and affordability.

The diagnostic devices identified in the landscape were evaluated against the TPP requirements and in discussion with experts, to evaluate which of the devices meet minimal and optimal requirements, with the aim to select two devices for a quantitative accuracy and system usability evaluation.

1.1 Study Rationale

While several technologies of multi-parameter POC devices capable of supporting diagnosis and monitoring of cardiometabolic diseases exist, their diagnostic accuracy is often not well evaluated outside of the manufacturer's laboratories and published independent evaluations can be rare, particularly in the settings of intended use. These settings are PHC facilities in varying climatic environments and with staff without specialist laboratory training.

Our study aims to evaluate the diagnostic accuracy of two cardiometabolic POC devices in a setting of intended use and performed by the intended user. The results will generate evidence on the expected accuracy of these POC devices and their performance in comparison to a standard laboratory method.

1.2 Background

Independent performance evaluation of POC devices have shown that many devices, regardless of their intended use, do not perform as well as the manufacturers' claims may suggest [7, 8]. There are a variety of reasons for this, including difference in skills levels of personnel who were involved in generating the data for the manufacturer's claims and who actually perform the test in a clinic, limited evaluation of samples from different geographical locations and thus potential interfering substances or less controlled environmental conditions (e.g. dust, heat and humidity).

Independent performance evaluations to assess clinical accuracy, as well as system usability are important to drive adoption of any technology, and even more so, if the technology is intended to move testing outside of the traditional setting, i.e. away from the central laboratory to the point-of-care. Many devices appear ideally suited for certain settings, however when it comes to actual implementation, the users often discover that the device and workflow do not meet their needs. The choice of a suboptimal device means badly invested resources and may lead to inappropriate use, resulting in fewer reliable tests for patients in the absence of alternatives. Data from real-world evaluations in settings of the intended use can support decision makers to select the right device.

The setting for this study will be a primary healthcare facility and a health post in Nepal, where study participants attend the facility in the context of the "Early detection and management of Chronic Kidney Diseases, Hypertension, Diabetes and Cardiovascular disease in Community in Nepal (KHDC-Nepal) program", conducted by the University Hospital of Geneva and the B.P. Koirala Institute of Health Science in Nepal.

1.3 Benefit/Risk Assessment

The risks for study participants are minimal as the study procedures only include collection of fingerstick blood and venous blood. Participants are facility attendees in the context of the above mentioned KHDC-Nepal early detection program, under which they have access to the relevant healthcare related to any clinical findings from this diagnostic accuracy study.

2 Study Objectives and Endpoints

TABLE 1: STUDY OBJECTIVE AND ENDPOINTS

Objectives	Endpoints
Primary	
1.1 To determine the accuracy of quantitative measurements of glucose, HbA1c, total cholesterol and creatinine* as measured in a healthcare setting with point-of-care multiparameter devices compared to a laboratory reference method.	1.1. Estimates of correlation and linear dependence between quantitative measurements of glucose, HbA1c, total cholesterol and creatinine evaluated in a healthcare setting with point-of-care multiparameter devices and in a laboratory reference assay. 1.2. Estimates of accuracy and limits of agreement for quantitative measurements of glucose, HbA1c, total cholesterol and creatinine

	evaluated in a healthcare setting with point-of-care multiparameter devices (compared to a laboratory reference assay).
Secondary	
2.1 To evaluate the operational characteristics and system usability of each cardiometabolic device when used in a PHC setting	2.1 Operational characteristics and usability of study devices: - Rate of invalid test results and error types - System usability score

*note: Creatinine is only available for one of the two investigational products

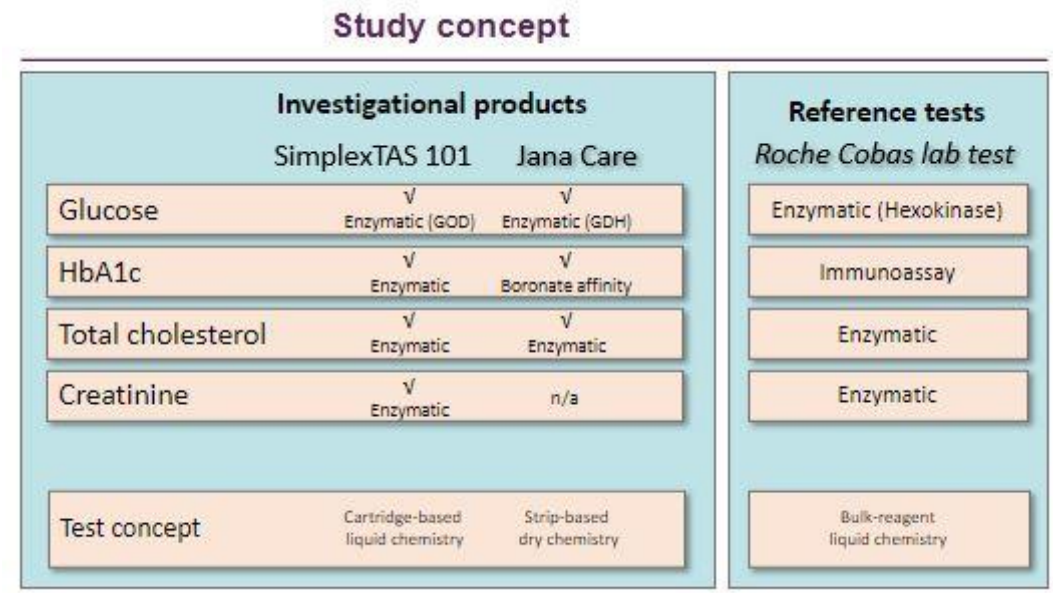
3 Study Design

3.1 General Design

This is a prospective quantitative accuracy study to assess the performance of clinical chemistry POC devices in comparison to a standard state of the art laboratory reference method available in the study country.

The general study concept is shown in Figure 1. For more information on the investigational product see section 4.1. Note that creatinine on the Aina Jana Care cardiometabolic platform is still in development and not available for evaluation.

FIGURE 1: STUDY CONCEPT, PARAMETERS EVALUATED AND REFERENCE TESTS



3.2 Scientific Rationale for Study Design

The study design was chosen with the objective in mind to evaluate the performance of POC devices compared to standard laboratory methods. In most countries, standard of care testing of the assessed parameters is done in centralized laboratories using venous whole blood. POC methods have several advantages over centralized methods, in that they use simpler sampling collection methods, i.e. fingerstick whole blood, do not require sample transport networks and can deliver results while the patient is at the healthcare facility. However, their adoption is often hampered by the perception that POC devices are less accurate, compared to centralized laboratory methods and the only comparison data available are generated by the manufacturers.

3.3 End of Study Definition

A participant is considered to have completed the study if he/she has completed the visit and all procedures as shown in the Schedule of Activities. The end of the study is defined as the date when all data entry is completed in the clinical study data base.

3.4 Study Population and Eligibility

The study will be conducted in two sites, at the Dhulabari primary healthcare centre (PHC) and at the Kakarvitta Health post in the rural area of Jhapa in Eastern Nepal. The study will be embedded in the KHDC-Nepal program, which has the objective to improve the health of the Nepalese population in Eastern Nepal through early detection and management of chronic non-communicable diseases. The program runs community awareness sessions and door-to-door visits to encourage members of the community to attend a screening visit at selected primary health facilities, health posts or at a pre-designated location. During this visit, people are screened for hypertension, diabetes, chronic kidney and cardiovascular disease, including (but not limited to) testing for glucose, lipids, HbA1c and creatinine.

Focus of the program are individuals ≥40 years of age based on the WHO risk prediction chart [9] and anyone ≥20 years is eligible for screening. In the program region, 50% of the population above 40 is expected to be screened, in which 25% may have at least one non-communicable disease (e.g. diabetes or elevated blood pressure) [10]. Anyone who screens positive for the NCDs in focus of the program is linked or referred to care at their local healthcare facility.

Community members who attend the Dhulabari PHC facility and the health post Kakarvitta in the context of the KHDC program will be invited to participate in the present study until the daily recruitment target across both sites is reached (5 participants per site/per day, or more if the site has capacity to test more participants per day). The Dhulabari PHC facility and the Kakarvitta health post run screening activities for the KHDC program during three hours in the morning. If interested and eligible study participants cannot be tested during these hours, they will be given appointments on a first-come-first-served basis for study participation. Additionally, KHDC program participants can be enrolled if they visit the Dhulabari PHC facility or Kakarvitta health post for a follow up appointment.

Results generated with the investigational products, or the reference assay will not be used for clinical decision making as the participants will have received these screening tests in the context of the KHDC program.

During the eligibility procedure, potential study participants will also be tested for haemoglobin to investigate if they suffer from abnormal haemoglobin values, which may have an impact on their HbA1c levels [11]. If potential participants are found to have haemoglobin levels of <8 g/dL, they will not be eligible for the study and will be referred by the local physician for follow up care.

Prospective approval of protocol deviations to recruitment and enrolment criteria, also known as protocol waivers or exemptions, is not permitted.

3.5 Inclusion Criteria

Participants are eligible to be included in the study only if all of the following inclusion criteria apply:

- 20 years or older (in line with KHDC eligibility age)
- Attending the Dhulabari PHC facility or Kakarvitta health post in the context of the KHDC program
- Haemoglobin levels ≥8 g/dL
- Able and willing to provide informed consent

3.6 Exclusion Criteria

Participants are excluded from the study if any of the following exclusion criteria apply:

- Inability to provide sufficient capillary or venous whole blood sample for all tests
- Haemoglobin levels < 8g/dL
- Anyone attending the Dhulabari PHC facility or Kakarvitta health post for other reasons than the KHDC program

3.7 Lifestyle Considerations

None

3.8 Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but do not subsequently undergo any of the study procedures. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Studies (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any serious adverse event (SAE).

4 Study Intervention

Study intervention is defined as any investigational intervention(s), marketed product(s), or medical device(s) intended to be used with a study participant according to the study protocol.

4.1 Investigational Product (or Study Intervention)

Table 2 shows test principle, sample types, sample volume and testing time for each of the parameters and investigational product, as well as the reference method.

TABLE 2: KEY CHARACTERISTICS OF THE INVESTIGATIONAL PRODUCT METHODS AND REFERENCE METHODS

	SimplexTAS 101									Jana Care									Reference method				
	Test principle	Sample type	Sample volume	Testing time	Measuring range	Correlation r2 (capillary blood)	Precision	%CV	Results plasma equivalent?	Test principle	Sample type	Sample volume	Testing time	Measuring range	Correlation r2 (capillary blood)	Precision	%CV	Results plasma equivalent?	Machine/test	Test principle	Sample type	Sample volume*	Measuring range
Glucose	Enzymatic (GOD)	cWB	10 µl	13 min	10-700 mg/dL (0.6-38.9 mmol/L)	y=1.0052x-0.1072	Low level: mean=79.18 mg/dL (SD:1.97)	2,50%		Enzymatic (GDH)	cWB	0.6 µl	10 sec	20-600 mg/dL (1.1-33.3 mmol/L)	y = 0.95x + 12.71	Low level: mean=97 mg/dL (SD:2.6)	1,80%		Roche	Enzymatic (Hexokinase)	NaF/Na2EDTA plasma	500 µl	0.11-41.6 mmol/L (2-750 mg/dL)
						0,9954	High level: mean=266.93 mg/dL (SD=4.74)	1,80%							0,99	High level: mean=492 mg/dL (SD=11.9)	2,40%						
HbA1c	Enzymatic	cWB	4 µl	13 min	4.0-15.0% (20-140 mmol/mol)	y=0.9933x+0.0877	Low level: mean=4.95 % (SD=0.18)	3,70%		Boronate afffinity	cWB	5 µl	3 min	4.0-15.0% (20-140 mmol/mol)	y = 0.973x + 0.349	Low level (1): mean=5.2% (SD=0.1)	2,50%		Roche	Immunoassay	K3EDTA vWB	500 µl	0.186-1.61 mmol/L (0.3-2.6 g/dL)
						0,9895	High level: mean=9.24 % (SD=0.22)	2,30%							0,981 (venous whole blood)	High level (4): mean=11.9% (SD=0.3)	2,80%						
Total cholesterol	Enzymatic	cWB	10 µl	13 min	20-500 mg/dL (0.5-12.9 mmol/L)	y=1.0035x-0.0700	Low level: mean=96.44 mg/dL (SD=3.99)	4,10%		Enzymatic	K2EDTA	15 µl	2 min	100-400 mg/dL (2.59-10.34 mmol/L)	y = 0.949x + 10.373	Low level: mean=128 mg/dL (SD=?)	3,90%		Roche	Enzymatic	Plain vial serum	500 µl	0.1-20.7 mmol/L (3.88-800 mg/dL)
						0,9922	High level: mean=235.49 mg/dL (SD=5.82)	2,50%							0,963	High level: mean=243 mg/dL (SD=?)	3,70%						
Creatinine	Enzymatic	cWB	20 µl	13 min	0.3-25.0 mg/dL (27-2210 µmol/L)	y=1.0171x-0.0862	Low level: mean=1.71 mg/dL (SD=0.07)	4,20%		n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a		Roche	Enzymatic	Plain vial serum	500 µl	5-2700 mmol/L (0.057-30.5 mg/dL)
						r2=0.9938	Hihg level: mean=5.10 mg/dL (SD=0.12)	2,30%															

GOD=glucose oxidase

GDH=glutamine dehydrogenase

cWB=capillary whole blood

* This sample volume includes the analyzer's dead volume

Medical device incidents, including those resulting from malfunctions of the device (or IVD), must be detected, documented and reported by the investigator at each site throughout the study (see Appendices).

4.2 Preparation/Handling/Storage/Accountability

Acquisition

Procurement of the investigational products will be done through FIND, who will coordinate shipments from the manufacturer. It is the responsibility of the study site to maintain an updated inventory of the study materials and to inform FIND immediately if additional materials are required.

The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for the investigational product received and any discrepancies are reported and resolved before its use.

Storage

Procedures for product storage and disposal will be described in the Study Manual.

The investigational product must be stored in a secured, environmentally controlled, and monitored (manual or automated) area in accordance with the labelled storage conditions with access limited to the investigator and authorized site staff.

Test Handling and Performance

Testing using the investigational products will be performed according to the manufacturer's instructions for use and as outlined in the study manual.

Only blood samples from participants enrolled in the study will be processed with the investigational product and only authorized site staff will be responsible for processing.

Accountability

The investigator is responsible for study intervention accountability, reconciliation, and record maintenance (i.e., receipt, reconciliation, and final disposition records). Investigational Product Accountability logs filled at each site will ensure the proper follow-up of the used, failed and remaining investigational products.

Further guidance and information for the final disposition of unused investigational product are provided in the study manual.

Export and Import Permits

Local sites are responsible for making import permit applications in a timely manner.

Quality Control Check for Incoming Shipments

Upon arrival of each new shipment of assays, the sites will conduct and document an incoming quality check following the Study Manual. New lots may only be used after this quality check is successfully passed.

Local procurement

Sites are responsible for assessing their needs and procuring any supplies, reagents and kits needed for the study that are locally available in order to include these costs in the study budget.

4.3 Minimisation of Error and Bias

To avoid the risk of sample and participant information mix ups, participants will be assigned a unique study ID and this number will be used in all study-related materials with participant information or sample material (either with specific labels or hand-written on e.g. cartridges without sufficient space for labels).

The risk of procedural errors for fingerstick blood collection and running of the assay on the investigational device will be reduced through the provision of training and competency assessment on the sample collection procedure and device operation. Training will be provided either by the manufacturers or by a manufacturer-trained FIND member of staff from the clinical trials unit. Training will be provided in person or remotely via live-video, in case of COVID-related travel restrictions.

The risk of procedural errors regarding the venous blood collection and the centrifugation are minimized since these procedures are undertaken by study personnel who perform phlebotomy and centrifugation as part of their daily routine. Further to this, they receive dedicated training on any study-specific procedures such as preparation of aliquots. With respect to mitigating of any sample mix-up the unique study ID label is used on all tubes (as well aliquots tubes). There is little risk for contamination as appropriate equipment is used, such as single-use pipette tips for aliquot preparation. All waste is discarded in biohazard waste bags.

There is little risk of bias in result interpretation, as the investigational devices produce alpha numeric results, which do not require interpretation by the user. Up to three members of staff, per site,will be trained to operate both investigational devices. For an individual participant, the same member of staff will collect samples for both devices for maximum comparability of results and to remove the risk of user-induced factors when comparing results from the same participant. Participants will be split approximately 50:50 between the two users and they will process participant samples interchangeably during the course of the study.

Participants ≥20 years of age are eligible for this study. The KHDC program focuses on members of the community who are 40 years or older, yet anyone ≥20 years can also be screened. However, this is not anticipated to introduce any bias, as the study purely focuses on the quantitative accuracy of the investigated parameters, which is unrelated to a participant's age.

4.3.1 Blinding Procedure

Blinding of operators to any health status or result is not necessary in this study, as all results will be generated automatically by the investigational device and do not require operator interpretation.

5 Participant Discontinuation/Withdrawal

5.1 Participant Discontinuation/Withdrawal from the Study

A participant may be withdrawn at any time at the discretion of the investigator for safety, behavioural, compliance, or administrative reasons.

If the participant withdraws consent for disclosure of future information, FIND may retain and continue to use any data collected before such a withdrawal of consent.

If a participant withdraws from the study, he/she may request destruction of any samples taken and not tested, and the investigator must document this in the site study records.

See Schedule of Activities for data and/or samples to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.

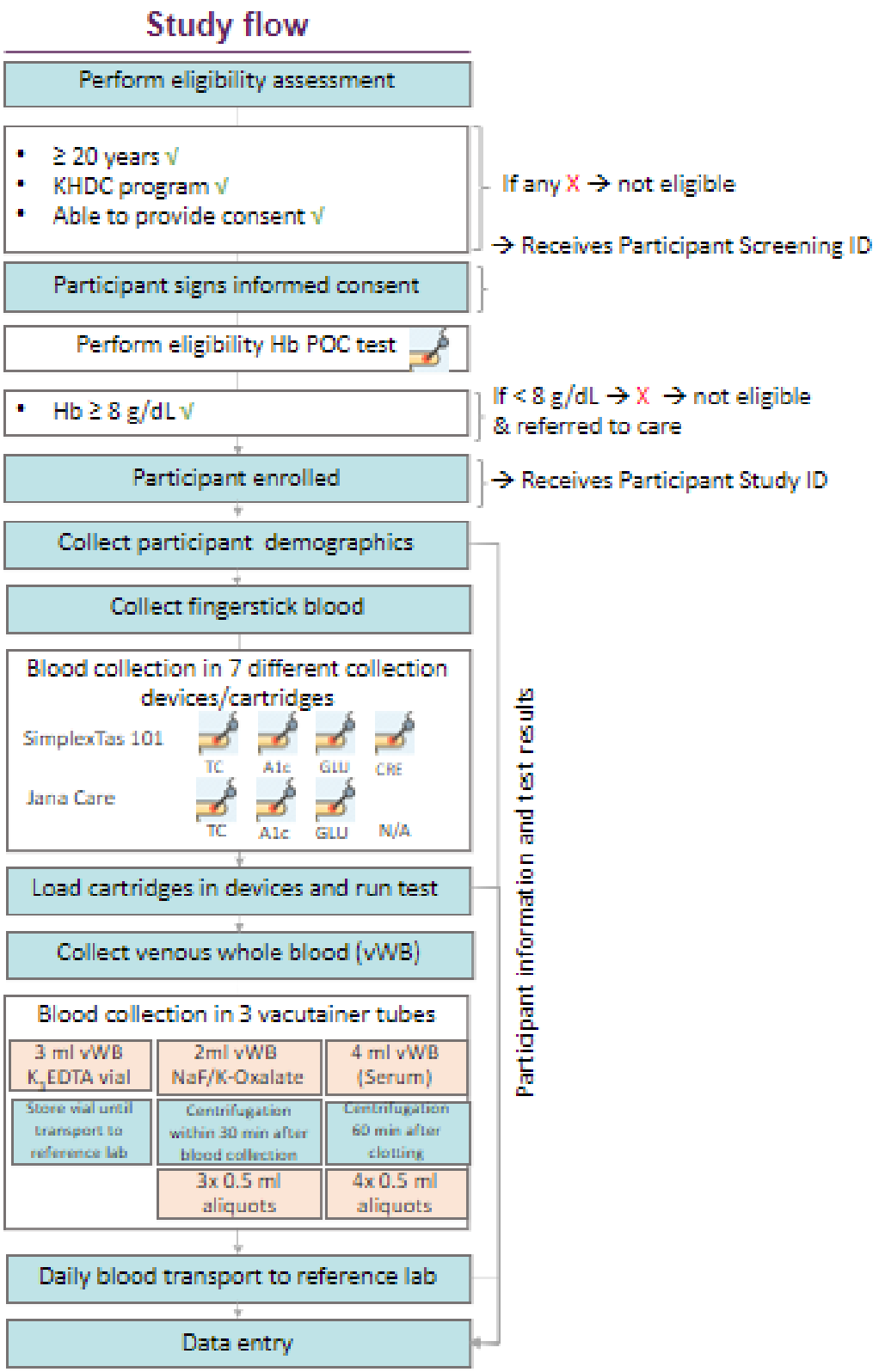
6 Study Procedures

Study procedures and their timing are summarized in the Schedule of Activities and outlined in Figure 2. Protocol waivers or exemptions are not allowed. Adherence to the study design requirements, including those specified in the Schedule of Activities, is essential and required for study conduct.

All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.

Procedures conducted as part of the participant's routine clinical management and obtained before signing of the Informed Consent Form (ICF) may be utilized for screening or baseline purposes provided the procedures met the protocol-specified criteria (see 6.1) and were performed within the time frame defined in the Schedule of Activities.

FIGURE 2: STUDY FLOW



6.1 Participant enrolment

Eligibility assessment and enrolment through signing of the informed consent form will be done at the PHC facility and the health post by trained staff. All individuals attending these facilities in the context of the KHDC program will be invited to participate in the study until the daily recruitment target of 10 participants (5 participants per site/per day, or more if the site has capacity to test more participants per day) is reached.

Individuals will be screened for eligibility and must provide their written consent to participate. After obtaining the signed consent, a participant screening ID is assigned to him/her for Haemoglobin testing and if eligible, a participant study ID is assigned to him/her and the participant is recorded in the enrolment log.

At enrolment, the following information will be collected for each participant, based on verbal information provided by the individual:

- Age
- Gender
- Pre-existing conditions (including but not limited to diabetes, hypertension, haemoglobinopathy, heart failure, dyslipidaemia, chronic kidney diseases, liver disease)
- Medications taken (including but not limited any glucose, lipid and blood pressure lowering medication in particular beta blockers and diuretics, traditional local medication (such as Hoodia, Gymnema, Aloe)
- Fasting status

Results of the following procedures as performed in the context of the KHDC program will also be collected from the medical records of each participant:

- BMI
- Smoking status, alcohol intake
- Diagnosis made of KHDC screening for chronic kidney diseases, hypertension, diabetes and cardiovascular disease

After recording the participant's demographic and clinical data in the dedicated Participant Worksheet, blood samples can be collected to perform all necessary study testing.

6.2 Specimen Collection, Handling, Transport and Storage

The maximum amount of blood collected from each participant over the duration of the study will not exceed 7 drops of fingerstick capillary blood (approximately 0.35 ml) for the study procedure, 1 drop of fingerstick capillary blood for the haemoglobin eligibility test and 9 ml of venous whole blood for the reference tests. Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

6.2.1 Capillary blood sample collection

Fingerstick capillary blood will be collected according to each manufacturer's IFU, e.g. with a provided capillary or sample collection device. The fingerstick capillary blood samples will be used immediately on the point-of-care assays.

6.2.2 Venous blood sample collection

The 9ml venous blood will be collected in NaF/K-Oxalate tubes for plasma (GLU), K2-EDTA tubes for whole blood (HbA1c) and in a plain vial for serum (CRE, CHOL). All tubes will be pre-labelled with a study specific identification label. Plasma will be separated by centrifugation within a maximum of 30 minutes from blood collection at the PHC facility and health post and aliquots will be prepared. Serum will be left to clot for a maximum of 60 min prior to centrifugation and serum aliquots will be prepared at the PHC facility and health post. The samples will be stored at 2-8°C until transfer to the BPKIHS reference lab. Once reference testing is completed, the left-over samples will be stored at 2-8°C until the results are validated according to the reference laboratories validation procedure. All left-over samples will be destroyed according to the laboratory's bio-safety procedures and sample destruction will be recorded.

6.3 Index Test and Reference Test Procedures

Test procedures for the reference tests and the POC index tests will be performed according to the manufacturer's IFUs, which are provided separately from this protocol.

6.3.1 Index tests procedure summary

SimplexTAS 101

The Tascom TAS101 sample cartridges contain an integrated sample collection device with a capillary tube. This tube is used to collect the required amount of fingerstick capillary whole blood by removing the collection device from the cartridge and holding it to the drop of blood on the finger. The filled collection device is subsequently re-inserted into the cartridge and loaded into the analyzer.

More information on appropriate sample collection techniques, loading of the cartridges and running of the test will be provided in the study manual and the manufacturer's analyzer handbook.

Sample volumes needed for each test do not exceed 20 µl per test and the exact volumes, as well as testing time and method are provided in Table 2.

JanaCare

The Aina JanaCare Monitoring System is intended to be used for quantitative measurement using a dry strip, a universal reader and a connected device. The required amount of fingerstick capillary whole blood are either collected directly on the test strip or via a small sample capillary before loading on the test strip. The test strip is subsequently inserted in the Aina universal reader device. The collected sample is then analyzed through the connected device.

More information on appropriate sample collection techniques and running of the test will be provided in the study manual and the manufacturer's analyzer handbook.

Even though a higher volume of blood collection is needed for performing Total Cholesterol parameter, the sample volumes needed for each test do not exceed 15 µl per test and the exact volumes, as well as testing time and method are provided in Table 2.

6.3.2 Reference tests

Reference testing will be done at the B.P. Koirala Institute of Health Sciences. The reference test for HbA1c will be the HbA1c Immunoassay (A1C) on the Roche cobas analyzer, which requires 3 ml of whole blood using K2-EDTA as anticoagulant. This is a validated sample type for this analyzer as per the manufacturer's instruction for use.

The reference tests for glucose, for total cholesterol and creatinine will be based on Enzymatic test principles, on the Roche cobas analyzer. Creatinine (CRE) and total Cholesterol (CHOL) are requiring 4 ml of whole blood (for 2ml of Serum) for analysis in total, and Glucose (GLU) 2 ml of whole blood (1.5 ml of Plasma). All sample types are validated by the manufacturers for use with the respective tests.

All reference tests will be performed according to the manufacturer's instruction for use and quality controls and calibrations for the tests are performed by the laboratory according to the manufacturers' recommendations (or based on the laboratories standard operating procedures for quality assurance of tests).

6.4 Training

All healthcare workers at the enrolment sites involved in participant testing will be trained in the procedures of the POC investigational devices, including instrument maintenance and control, sample collection and testing workflow. On-site Training or Online Training will be performed by the manufacturers or by the FIND study manager after having received training from the manufacturer.

Healthcare workers involved in participant eligibility assessment, participant information and informed consent as well as data management will be trained on the procedures specifically by the FIND study manager.

Proficiency will be documented in a training log.

6.5 Genetic Analysis

Genetic data will not be evaluated in this study.

6.6 Experimental Biomarkers

Experimental biomarkers are not evaluated in this study.

6.7 Other Tests (Specify)

Participants will have been tested for haemoglobin levels during the eligibility assessment. The results will be used in the statistical analysis to correlate haemoglobin levels with HbA1c results. The test will be performed with the Hemocue Hb301+ point-of-care hemoglobin analyzer requiring a fingerstick blood sample.

6.8 Safety Assessments

There will be no planned safety assessments as the risks for the participants are considered minimal (see section 1.3).

6.9 Other Study Procedures

No other study procedures are planned.

7 Safety and Incident Reporting

Given that this is a quantitative accuracy study of clinical biochemistry point-of-care assays, the probability of an adverse event (AE) or a serious adverse event (SAE) occurring to a study participant to be associated with the investigational products is extremely low (see Appendix 1 for definitions of AE or SAE). Considering this, only deaths occurring between the start of the fingerstick blood collection and until the participant leaves the study will be recorded on a standardized form and reported to FIND by the investigator within 24 hours of becoming aware.

7.1 Medical Device Incidents (including Malfunctions)

Medical devices are being provided for use in this study for the purpose of assessing their diagnostic accuracies. In order to fulfil regulatory reporting obligations worldwide, the investigator is responsible for the detection and documentation of events meeting the definitions of incident or malfunction that occur during the study with such devices.

The definition of a Medical Device Incident can be found in Appendix 2.

Examples of a medical device incident for this study could be:

- A broken sample collection device (if provided)
- A broken or malfunctioning capillary tube or pipette provided

NOTE: Incidents fulfilling the definition of an SAE will also follow the processes outlined above and in Appendix 2 of the protocol.

7.2 Time Period for Detecting Medical Device Incidents

Medical device incidents or malfunctions of the device that result in an incident will be detected, documented, and reported during all periods of the study in which the medical device is used.

If the investigator learns of any incident at any time after a participant has been discharged from the study, and such incident is considered reasonably related to a medical device provided for the study, the investigator will promptly notify FIND.

The method of documenting Medical Device Incidents is provided in Appendix 2.

7.3 Follow-up of Medical Device Incidents

All medical device incidents involving an SAE will be followed and reported in the same manner as other SAEs (see Section 7.1.2). This applies to all participants, including those who discontinue study intervention.

The investigator is responsible for ensuring that follow-up includes any supplemental investigations as indicated to elucidate the nature and/or causality of the incident.

New or updated information will be recorded on the originally completed form with all changes signed and dated by the investigator.

7.4 Reporting of Medical Device Incidents to FIND

Medical device incidents will be reported to FIND within 24 hours after the investigator determines that the event meets the protocol definition of a medical device incident.

The Medical Device Incident Report Form will be sent to FIND by email. If email is unavailable, then a mobile phone photo and text messaging should be utilised.

The same individual(s) will be the contact for the receipt of medical device incident reports and SAE reports.

7.5 Regulatory Reporting Requirements for Medical Device Incidents

The investigator will promptly report all incidents occurring with any medical device provided for use in the Study in order for FIND to fulfil the legal responsibility to notify appropriate regulatory authorities and other entities about certain safety information relating to medical devices being used in clinical studies.

The investigator, or responsible person according to local requirements (e.g., the head of the medical institution), will comply with the applicable local regulatory requirements relating to the reporting of incidents to the IRB/IEC.

8 Statistical Considerations

This section provides summary of the planned statistical analyses of the primary and secondary endpoints, as well as details on the sample size calculation. A Statistical Analysis Plan (SAP) will be written before the start of recruitment and will describe the analysis strategy in detail. Analysis of the exploratory objectives will be described in the SAP.

8.1 Populations for Analyses

For purposes of analysis, the following populations will be defined as per Table 3.

TABLE 3: POPULATION FOR ANALYSIS

Population	Description
Enrolled	All participants who sign the informed consent
Evaluable/Per Protocol Population (PP)	All participants who fully complied with the protocol and for whom index test results and reference test results are available for all tests.
Partially Compliant Population (PCP)	All participants who complied partially with the protocol, i.e. those for whom index test results and reference test results are available but not in a complete form (e.g. missing one POC result)

8.2 Statistical Analyses

8.2.1 Analysis of primary and secondary outcomes

The primary and secondary outcomes of the study are presented in the Table 4.

TABLE 4: ENDPOINTS AND ANALYSIS METHOD

Endpoints	Analysis method
Primary	
1.1 Estimates of correlation and linear dependence between quantitative measurements of glucose, HbA1c, total cholesterol and creatinine evaluated in a healthcare setting with point-of-care multiparameter devices and in a laboratory reference assay.	1.1 Point estimates of Pearson correlation coefficient, coefficient of determination (R^2), intercept and slope coefficient of linear regression (with 95% confidence intervals), will be computed for all biomarkers and devices compared to the reference assay.
1.2 Estimates of accuracy and limits of agreement for quantitative measurements of glucose, HbA1c, total cholesterol and creatinine evaluated in a healthcare setting with point-of-care multiparameter devices (compared to a laboratory reference assay).	1.2 Point estimates of fixed and proportional bias (with 95% confidence interval), coefficient of variation and limits of agreement, calculated via Bland-Altman analysis in absolute and relative units, will be computed for all biomarkers and devices compared to the reference assay.
Secondary	

2.1 Operational characteristics and usability of study devices: - Rate of invalid test results and error types - System usability score	2.1 Proportion of invalid tests per parameter (with 95% confidence interval based on Wilson's score method) will be computed for each device. System usability score will be analyzed with descriptive statistics.

Point estimates of correlation between concentrations of biomarkers, measured with the POC devices and reference assay, will be calculated based on Pearson's method separately for each device and marker type. The dependence between the measurements of POC devices and the reference method will be visualized with the use of scatter plots and analyzed using linear regression. Point estimates of intercept and slope coefficient, with 95% confidence intervals, and coefficient of determination (R^2) will be computed separately for each device and marker type.

To evaluate the systemic deviation of POC device measurements from the established reference assay, Bland-Altmann analysis will be performed for each marker type and device. The deviation will be visualized with the Bland-Altman plot in absolute and relative units. Point estimates of fixed bias (mean difference between measurements) and proportional bias (dependence of the difference on concentration level), with 95% confidence intervals, will be computed. Standard deviation of the difference between the measurements of POC device and reference assay will be evaluated, along with the coefficient of variation and 95% prediction interval (limits of agreement) of the error. All calculations will be performed in absolute and relative units.

Secondary endpoints include the evaluation of system usability score and proportion of invalid tests for POC devices. The mean and 95% confidence interval will be estimated for these characteristics separately for each device. Confidence interval for the proportion of invalid tests will be calculated based on Wilson's score method.

8.2.2 Safety Analysis

No safety analysis will be performed as the risks for the participants are considered minimal (see section 1.3).

8.2.3 Other Analyses

Descriptive statistics tables will be generated to summarize the characteristics of the samples in the different populations. The number of samples included and excluded will be reported, and among the included samples, information will be broken down by gender, age group, medication taken, disease status (pre-existing condition and new diagnosis in KHDC program), BMI, smoking/alcohol. Results will be reported either in absolute numbers (e.g. number of subjects in a group) or summarized by mean, standard deviation, minimum, median, maximum and quartiles.

The information may be used for interpretation of the POC test performance.

8.3 Planned Interim Analyses

No interim analyses are planned for this study.

8.3.1 Data Monitoring Committee (DMC)

There will be no data monitoring committee. Interim data monitoring will be conducted by FIND.

8.4 Sample Size Determination

Available data from an external evaluation study of the performance of the Tascom and Jana Care assays, showed Pearson correlation coefficients greater than 0.98 for all markers compared to the reference laboratory standard [xxx = reference corresponding to Excel table]. The precision estimated as the standard deviation of difference of measurements compared to reference divided by the mean concentration (%CV) was in range of 1.8-4.1% for SimplexTas 101 and 1.9-3.9% for Jana Care, depending on the marker and its concentration.

TABLE 5: INVESTIGATIONAL PRODUCTS PERFORMANCE CLAIMS AS PER IFU

Assay	ρ, Pearson correlation	Precision (%CV) at low and high concentrations
SimplexTAS 101 Glucose	0.998	Low = 2.5% High = 1.8%
SimplexTAS 101 HbA1c	0.995	Low = 3.6% High = 2.4%
SimplexTAS 101 Total cholesterol	0.996	Low = 4.1% High = 2.5%
SimplexTAS 101 Creatinine	0.997	Low = 4.1% High = 2.4%
Jana Care Glucose	0.995	Low = 2.7% High = 2.4%
Jana Care HbA1C	0.99	Low = 1.9% High = 2.5%
Jana Care cholesterol	0.981	Low = 3.9% High = 3.7%

Considering the possibility of a lower performance of POC device outside of the manufacturer's laboratories, the Pearson's correlation coefficient and precision were conservatively assumed to be 0.9 and 5%, respectively. Based on this assumption, at least 337 samples (for each marker and device) will be needed to detect statistically significant ±1.5% fixed bias of POC measurements compared to the reference (using two-tailed t-test with 80% power and 5% significance level).

To improve the precision of the test, the number of samples per marker analyzed in this study was increased to 400 per device, recruited at two trial sites. Assuming that the expected Pearson's correlation coefficient (ρ) between POC and reference measurements is 90%, 95% or 99%, t*he proposed sample size will allow to estimate ρ with the 95% confidence interval of 88–91.7%, 93.9–95.9% and 98.8–99.2%, respectively.*

8.5 Statistical software

The analysis will be performed using the R statistical language, version 3.6 or higher, and Microsoft Excel (for the initial inspection of the data) version 16.16 or higher.

9 Regulatory and Ethical Considerations

Ethical conduct of the study; i.e. that the study will be conducted in accordance with the Protocol, all ICH and GCP regulations governing clinical study conduct; ethical principles that have their origin in the Declaration of Helsinki, and all applicable local laws and regulations.

Informed Consent; i.e. that the Investigator or his/her representative will explain the nature of the study to the subject, and answer all questions regarding this study, prior to obtaining Informed Consent

Participant confidentiality; i.e. that the Investigators must ensure that the subject's anonymity will be maintained.

FIND should ensure that the Investigator(s)/institution(s) will permit study-related monitoring, audits, IEC/IRB review, and regulatory inspection(s), providing direct access to source data/documents. This is mentioned in the Statement of Investigator above.

9.1 Regulatory and Ethics Approvals

This study will be conducted in accordance with the protocol and with the following:

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki
- Applicable Good Clinical Practice Guidelines: ICH GCP E6 (R2)
- Applicable laws and regulations

The protocol, protocol amendments, ICF and other relevant documents (e.g. advertisements) must be submitted to an IRB/IEC by the investigator and reviewed and approved by the IRB/IEC before the study is initiated. A copy of the IRB/IEC approval letter will be filed in the investigator site file.

FIND-approved versions of an amended study protocol must be signed by the Investigator(s). Any substantial amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants. Protocol amendments restricted to clerical edits only will be provided to the study sites and submitted to the IRB/IEC for informational purposes.

The investigator will be responsible for the following:

- Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC
- Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures
- Providing oversight of the conduct of the Study at the site and adherence to requirements of ICH guidelines, the IRB/IEC, the WHO Good Clinical Laboratory Practice (GCLP), and with applicable national regulations.

9.2 Financial Disclosure

Investigators and sub-investigators will provide FIND with sufficient, accurate financial information as requested to allow FIND to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities.

9.3 Informed Consent Process

The investigator or his/her representative will explain the nature of the study to the participant or his/her legally authorized representative in a language understandable to him/her and answer all questions about the study.

Participants must be informed that their participation is voluntary. Participants or their legally authorized representative will be required to sign and date a statement of informed consent that meets the requirements of local regulations, ICH guidelines and the IRB/IEC or study centre.

There must be evidence that written informed consent was obtained before the participant was enrolled in the study, and ample time was given to participant to consent. The date the written consent was obtained (as well as the time, ideally) must be recorded. The authorised person obtaining the informed consent must also sign and date the ICF.

Illiterate participants must provide a thumbprint on the ICF and the ICF signed and dated by an impartial witness.

Participants must be re-consented to the most current version of the ICF(s) during their participation in the study. A copy of the ICF(s) will be given to the participant or the participant's legally authorized representative.

A participant who is rescreened is not required to sign another ICF if the rescreening occurs within (3) days from the previous ICF signature date.

9.4 Data Protection

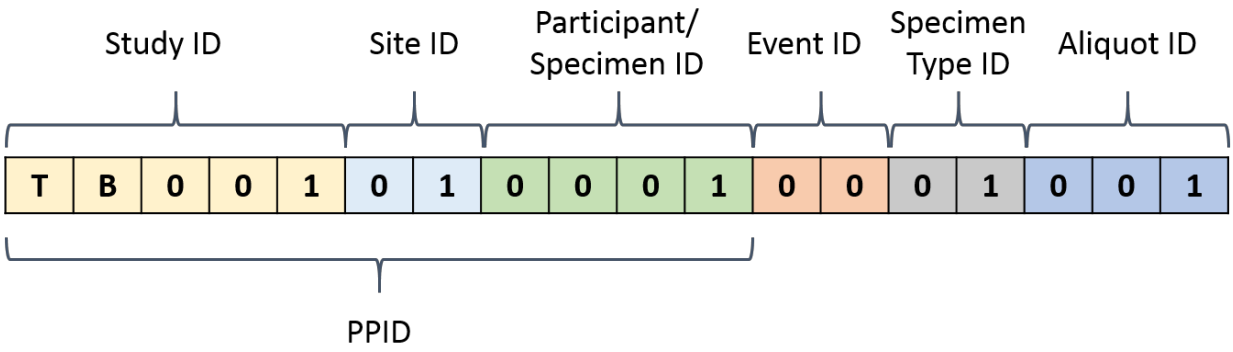
Participants will be assigned a unique study identifier generated by FIND once enrolled in the study (see example in Figure 3). During the screening process, a separate unique screening identifier will be assigned to each participant. The purpose of the screening identifier is to link participants who did not pass the screening process to entries in the enrolment log. Only participants who pass the screening process (including meeting haemoglobin enrolment criteria) will be assigned a unique study identifier.

Any participant records or datasets that are transferred to FIND will contain the identifier only; participant names or any information, which would make the participant identifiable, will not be transferred.

The participant will be informed that his/her personal study-related data will be used by FIND in accordance with local data protection law. The level of disclosure must also be explained to the participant.

The participant will be informed that his/her medical records may be examined by quality assurance (QA) auditors or other authorized personnel appointed by FIND, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

FIGURE 3: PARTICIPANT ID EXAMPLE



10 Data Handling and Record Keeping

FIND is responsible for the data management of this study including quality control (QC) checks of the data and assessment of overall protocol compliance. All participant data relating to the study will be recorded in source documents and transcribed on to a paper Case Report Form (CRF) by study site staff. Data will then be entered from the paper CRF into FIND's online clinical study platform (OpenClinica Enterprise Edition *version 4.0*). The investigator is responsible for verifying that data entries are accurate and correct.

Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the investigator for 10 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of FIND. No records may be transferred to another location or party without written notification to FIND.

10.1 Source Data and Source Documents

Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. The investigator/institution should maintain adequate and accurate source documents and study records that include all pertinent observations on each of the site's study participants (source data). Source documents are filed at the investigator's site.

Source data should be attributable, legible, contemporaneous, original, accurate and complete. Changes to source data should be traceable, should not obscure the original entry and should be explained if necessary.

The definition of what constitutes source data can be found in Table 3.

The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to participant medical records and source documents used for this study.

Participant data will consist of participant demographics, clinical examination and laboratory test results. Information on demographics will be recorded directly into the CRF (source data). Results of the clinical examination under the KHDC program will be transcribed from the program or medical records (source data) into a study-specific paper CRF. Results from the POC devices and the reference analyzers will also be transcribed into study-specific paper CRFs from the device/analzyer print-outs/electronical files (source data).

Any source data directly entered into the paper CRF must be signed and dated by the person who generated the data.

TABLE 3: TYPES OF SOURCE DATA AND CRFS.

Type of data	Source data (original place of data)	CRF
Demographics	Paper CRF	Study-specific paper CRF: **Clinical**
Medical information	Paper CRF	Study-specific paper CRF: **Clinical** (same as above)
Specimen collecting time and date	Paper CRF	Study-specific paper CRF: Specimen collection
POC test result	Device print-out or electronic file	Study-specific paper CRF: **POC results**
Reference test result	Device print-out or electronic file	Study-specific paper CRF: **Reference results**
System usability score	Paper CRF	Study-specific paper CRF: **SUS**

10.2 Data Management

Data Management procedures at FIND, including the setup of the database, programming edit and range checks and querying, are described in the Data Management Plan.

Site staff will be responsible for entering their data from a paper CRF into OpenClinica. Detailed timelines for data transfer will be provided in the Study Manual. Data will be cleaned of errors by FIND throughout the study as it is captured electronically.

The investigator is responsible for verifying that data entries are accurate and correct. Data entered in the OpenClinica database must be consistent with the source documents or the discrepancies must be explained.

The site will be provided with individual password-protected accounts to access OpenClinica, following a training session given by FIND.

OpenClinica provides an audit trail system recording all data entries/changes and queries between FIND and the site. Data entry training will be provided by FIND, either on site or remotely sharing screen through Skype or any other similar system.

No information concerning the study or the data generated from the study will be released to any unauthorized third party without prior written approval of FIND.

11 Quality Management

Quality Management for this study consists of Quality Control activities, training and capacity building provided by FIND (or designee) to the investigational sites, as well as the use of Standard Operating Procedures, Work Instructions, Tools and Templates. Prior to study start FIND will verify that the reference laboratory has adequate quality management procedures in place to ensure

reliability of test results. This will be verified by reviewing relevant quality management system (QMS) documents of the laboratory and verifying evidence of adherence through e.g. availability of analyser calibration and control results.

Training on the protocol, GCP and the use of the POC tests will be provided by FIND. A study Manual, which describes all of the sample testing procedures, will be provided by FIND prior to the commencement of the study. Training on the EDC system will be provided by FIND Data Management prior to first participant enrolment.

11.1 Quality Control (monitoring)

Quality control should be applied to each stage of data handling to ensure that all data are reliable and have been processed correctly. The investigational site is responsible for performing regular quality control checks on the data they generate.

FIND will perform risk-based monitoring of this study, and associated quality control checks, as described in the monitoring plan. Study monitors will perform source data review and source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

11.2 Quality Assurance (auditing)

As part of routine quality assurance, FIND or designee may conduct an audit of the investigational site.

11.3 Study and Site Closure

FIND reserves the right to close the study site or terminate the study at any time for any reason at its sole discretion. Investigational sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected or destroyed.

The investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for early closure of a study site by FIND are described in the contractual agreement.

12 Publication Policy

Data obtained from participation in this study are considered confidential and may be used to support market approval. The investigators must adhere to the non-disclosure requirements set forth in the FIND agreement.

The investigator is obligated to provide FIND or its designee with complete test results and all data obtained in this study. Only FIND may make information obtained during this study available to other investigators and third parties, including regulatory agencies.

Authorship for scientific publication of the study results will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements, as described in the publication policy section of the contractual agreement.

13 References

1. Jamison, D.T., *Disease Control Priorities, 3rd edition: improving health and reducing poverty.* Lancet, 2018. **391**(10125): p. e11-e14.
2. IHME. *Institute for Health Metrics, Global Burden of Disease Compare Viz Hub*. 2019 [cited 2021; Available from: https://vizhub.healthdata.org/gbd-compare/.
3. FIND. *Landscape of Point-of-Care Devices for Testing of Cardiometabolic Diseases*. 2020 [cited 2021 17-Mar]; Available from: https://www.finddx.org/wp-content/uploads/2020/02/Landscape-of-poc-devices-for-cardiometabolic-diseases-28FEB2020.pdf.
4. WHO. *Package of Essential Noncommunicable (PEN) Disease Interventions for Primary Health Care in Low Resource Settings*. 2020 [cited 2021 17-Mar]; Available from: https://www.who.int/publications/i/item/who-package-of-essential-noncommunicable-(pen)-disease-interventions-for-primary-health-care.
5. WHO. *The selection and use of essential in vitro diagnostics - TRS 1031*. 2021 [cited 2021 17-Mar]; Available from: https://www.who.int/publications/i/item/9789240019102.
6. Vetter, B., Beran, D., Boulle, P., Chua, A., delaTour, R., Hattingh, L., Perel, P., Roglic, G., Sampath, R., Woodman, M., Aebischer-Perone, S., *Development of a target product profile for a point-of-care cardiometabolic device.* BMC Cardiovascular Disorders, 2021. **Manuscript submitted**.
7. Drain, P.K., et al., *Diagnostic point-of-care tests in resource-limited settings.* Lancet Infect Dis, 2014. **14**(3): p. 239-49.
8. Hirst, J.A., et al., *Performance of point-of-care HbA1c test devices: implications for use in clinical practice – a systematic review and meta-analysis.* Clin Chem Lab Med, 2017. **1**(2): p. 167-180.
9. Group, W.C.R.C.W., *World Health Organization cardiovascular disease risk charts: revised models to estimate risk in 21 global regions.* Lancet Glob Health, 2019. **7**(10): p. e1332-e1345.
10. WHO. *Non Communicable Disease Factors: STEPS Survey Nepal 2013*. 2013 [cited 2021 17-Mar]; Available from: https://www.who.int/ncds/surveillance/steps/2012-13_Nepal_STEPS_Report.pdf.
11. WHO, *Use of Glycated Haemoglobin (HbA1c) in the Diagnosis of Diabetes Mellitus* 2011, World Health Organization: Geneva.

14 Appendices

Appendix 1: Safety Definitions and Reporting

Adverse Event (AE) Definition
• An AE is any unfavourable and unintended sign (including abnormal laboratory finding), symptom or disease temporally associated with the use of an investigational product, whether or not related to the investigational product.

Serious Adverse Event (SAE) Definition:
a. Results in death
b. Is life-threatening The term 'life-threatening' in the definition of 'serious' refers to an event in which the participant 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.
c. Requires inpatient hospitalization or prolongation of existing hospitalization In general, hospitalization signifies that the participant has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfils any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious. Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.
d. Results in persistent disability/incapacity • The term disability means a substantial disruption of a person's ability to conduct normal life functions. • This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhoea, influenza, and accidental trauma (e.g., sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
e. Is a congenital anomaly/birth defect
f. Other situations: • Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious. Examples of such events include intensive treatment in an emergency room or at home for allergic bronchospasm or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

The Protocol Author is responsible for verifying safety reporting requirements. SAE Reporting to FIND may differ than described below. If that is the case, describe the procedure in detail.

SAE Reporting to FIND
• The SAE Report must be sent to the FIND Head of Program and Study Manager via e-mail, marked High Priority, with a follow up call to ensure receipt. • Initial notification via telephone does not replace the need for the investigator to complete and sign the SAE Report within the designated reporting time frames. • Contacts for SAE reporting can be found on the front of the protocol.

Appendix 2: Incident Definition and Reporting

Verify with the IVD manufacturer what the procedure will be for reporting incidents to them and describe below.

Medical Device/IVD Incident Definition
• A medical device incident is any malfunction or deterioration in the characteristics and/or performance of a device or IVD as well as any inadequacy in the labelling or the instructions for use which, directly or indirectly, might lead to or might have led to the death of a participant/user/other person or to a serious deterioration in his/her state of health. • Not all incidents lead to death or serious deterioration in health. The non-occurrence of such a result might have been due to other fortunate circumstances or to the intervention of health care personnel.

It is sufficient that:

- An incident associated with a device happened.

  AND

- The incident was such that, if it occurred again, might lead to death or a serious deterioration in health.

A serious deterioration in state of health can include any of the following:

- Life-threatening illness
- Permanent impairment of body function or permanent damage to body structure
- Condition necessitating medical or surgical intervention to prevent one of the above
- Foetal distress, foetal death, or any congenital abnormality or birth defects

Medical Device Incident Documenting
• Any medical device incident occurring during the study will be documented in the participant's medical records, in accordance with the investigator's normal clinical practice, and on the appropriate form of the CRF. • For medical device incidents fulfilling the definition above, complete the SAE Report Form. • It is very important that the investigator provides his/her assessment of causality (relationship to the medical device provided by FIND) and describes any corrective or remedial actions taken to prevent recurrence of the incident. • A remedial action is any action other than routine maintenance or servicing of a medical device where such action is necessary to prevent recurrence of an incident. This includes any amendment to the device design to prevent recurrence.

Appendix 3: Protocol Amendment Summary Table

The Protocol Amendment Summary of Changes Table for the current amendment is located directly before the Abbreviations section.

Amendment [v2.0]: *30-MAR-2022*

Overall Rationale for the Amendment

After the Site Initiation Visit, several technical points had to be revised.

Section # and Name	Original description (V1.0)	Description of Change (V2.0)	Brief Rationale
Institutions/Organizations/Partners Involved in the Study	Sub PI: Dr Anup Ghimire	Name of Sub-Principal Investigator in Nepal Changed.	Dr. Anup Ghimire was not available anymore to follow this study and is replaced by Dr. Vijay Khanal & Dr. Sagar Poudel.
4.3 Minimization of Error and Bias	No mention about risk mitigation on venous blood collection and centrifugation	The sentence “The risk of procedural errors regarding the venous blood collection and the centrifugation are minimized since these procedures are undertaken by study personnel who perform phlebotomy and centrifugation as part of their daily routine. Further to this, they receive dedicated training on any study-specific procedures such as preparation of aliquots. With respect to mitigating of any sample mix-up the unique study ID label is used on all tubes (as well aliquots tubes). There is little risk for contamination as appropriate equipment is used, such as single-use pipette tips for aliquot preparation. All waste is discarded in biohazard waste bags.” Was added	Additional information for risk mitigation on this procedure was required.
6. Study Procedure; Study Flow	On the Study flow, the Glucose was mentioned as 3ml of venous Whole Blood to be collected.	The study flow graph was changed according to the new volumes collected	2ml instead of 3ml venous blood collection for Glucose and the vials names had to be changed on the graph as well.
6.1 Participant enrolment	“Ethnicity” was mentioned as an information requested to our participants.	“Ethnicity” was deleted	This is not an information we request from our participants, since all of them are Nepali.

6.2 Specimen Collection, Handling, Transport and Storage	7 drops of blood (was mentioned as of 0.2 ml), and 10 ml in total.	7 drops of blood is not 0.2ml, but 0.35 ml (counting 1 drop as 0.05ml). 9ml of venous whole blood instead of 10ml	Due to a miscalculation, 7 drops of blood is not 0.2ml, but 0.35 ml (counting 1 drop as 0.05ml). And 9ml of venous whole blood instead of 10ml, even if initially we were concerned that we would not have enough plasma for making aliquots, we saw that 2ml is sufficient volume.
6.2.1 Capillary blood sample collection	The sentence "All sample cartridges will be pre-labelled manually with the study-specific participant number." Was mentioned	The sentence "All sample cartridges will be pre-labelled manually with the study-specific participant number. " was deleted	Refer to Protocol Deviation. The sample cartridges are not pre-labelled manually with the study-specific participant number, since there is no need to (participant come one after the other) and it is already entered electronically into the POC machine.
6.2.1 Venous blood sample collection	Before the temperature rate was written as "4°C"	Instead of 4°C we added "2-8°C"	This is the usual range of a fridge to operate.
6.2.2 Venous blood sample collection	Before the vacutainer mentioned on the protocol for Glucose collection was NaF/Na2EDTA and for HbA1c K3EDTA.	The vacutainers to be used for venous blood collection of Glucose are NaF/K-Oxalate and not NaF/Na2EDTA. And for HbA1c, it is K2EDTA and not K3EDTA.	This applies to all samples in the trial, the change was made prior the start of recruitment. According to the package inserts these vacutainer are compatible for Roche Cobas. Refer to protocol deviation.
6.2.2 Venous blood sample collection	The volume of blood collection for Glucose was mentioned as 3ml.	The volume of blood collection for Glucose in NaF/K-Oxalate is not 3ml but 2ml instead.	Initially we were concerned that we would not have enough plasma for making aliquots, we saw that 2ml is sufficient volume. This change was made prior the start of recruitment. Refer to protocol deviation.
6.2.2 Venous blood sample collection	The clotting time was initially stated as for a maximum of 30 minutes.	Change of the clotting time for the Serum Total Cholesterol & Creatinine Venous blood collection. It is not 30 min but 60 min.	This is the recommended time on BD package inserts.
6.7 Other Tests (Specify)	Initially it was mentioned Hb201+	Hb201+ was changed into Hb301+	Correction of a mistake: The HemoCue machine is the Hb301+ and not as initially written Hb201+
Other sections	Minor formulation issues on v1.0	Minor formulation and re-phrasing	Administrative changes for clarification purposes