

SIREN  
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# SIREN: the journey towards accurate comprehensive stroke phenotyping in Africa

Stroke Investigative Research and Educational Network  
(SIREN)  
Investigators



Fifth H3 Africa Consortium Meeting, November 7-10, 2014, Dar es Salaam

# Background

- Stroke epidemic in sub-Saharan Africa
- Need to characterize this epidemic
- Epidemiologic, phenotypic and genomic characterization
- SIREN : a response to the clarion call.

# The SIREN Partners



## Cardiovascular Topics

# Understanding the rise in cardiovascular diseases in Africa: harmonising H3Africa genomic epidemiological teams and tools

Mayowa O Owolabi, George A Mensah, Paul L Kimmel, Dwomoa Adu, Michele Ramsay, Salina P Waddy, Bruce Ovbiagele, Cristina Rabadan-Diehl, Rebekah Rasooly, Sally N Akarolo-Anthony, Charles Rotimi as members of the H3Africa Consortium

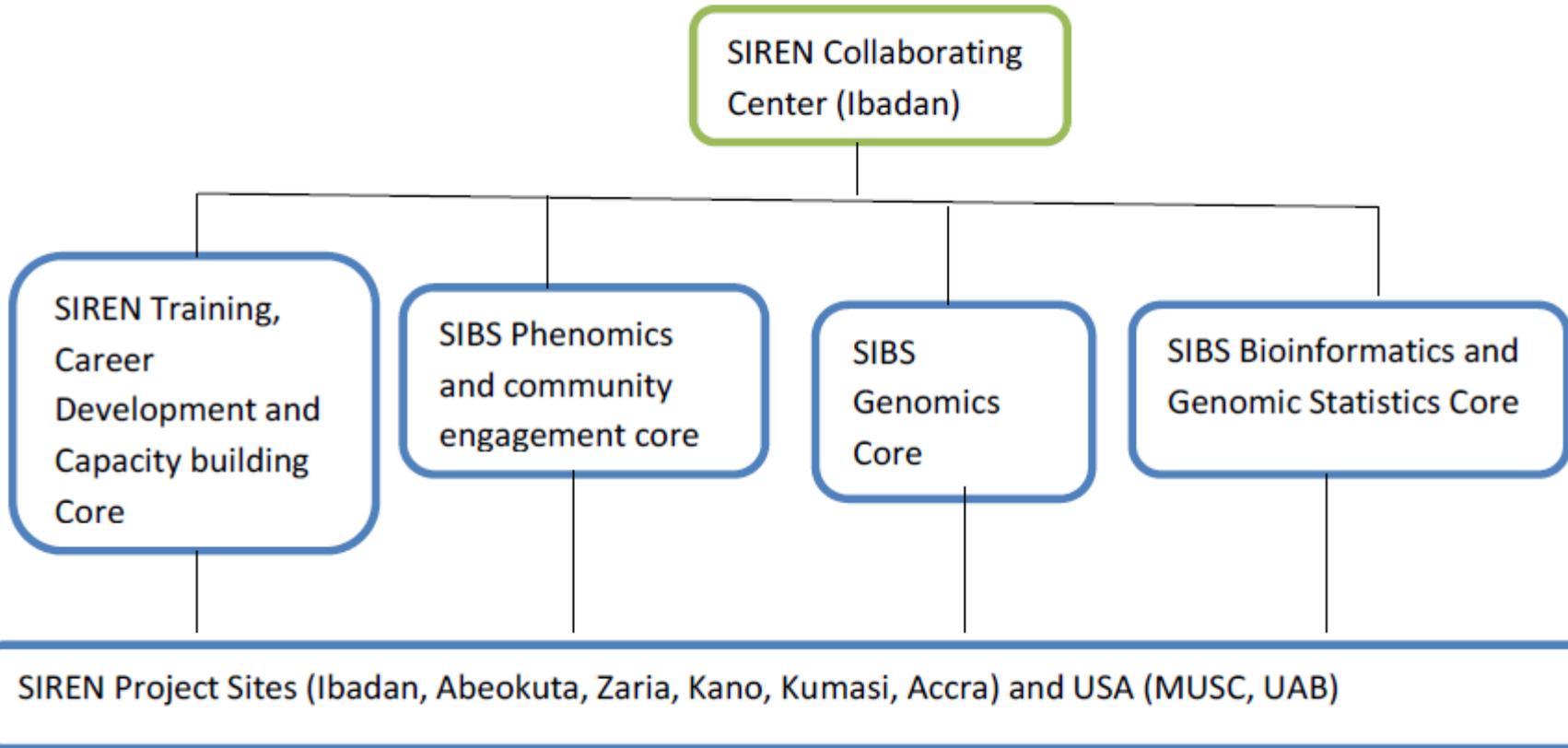
# SIREN : Overarching Goal

- ✓ To evaluate the *genomic and environmental risk factors for stroke in SSA*, while simultaneously **building sustainable capacities** in phenomics, biobanking, genomics, biostatistics and bioinformatics.

# SIREN : Component Projects

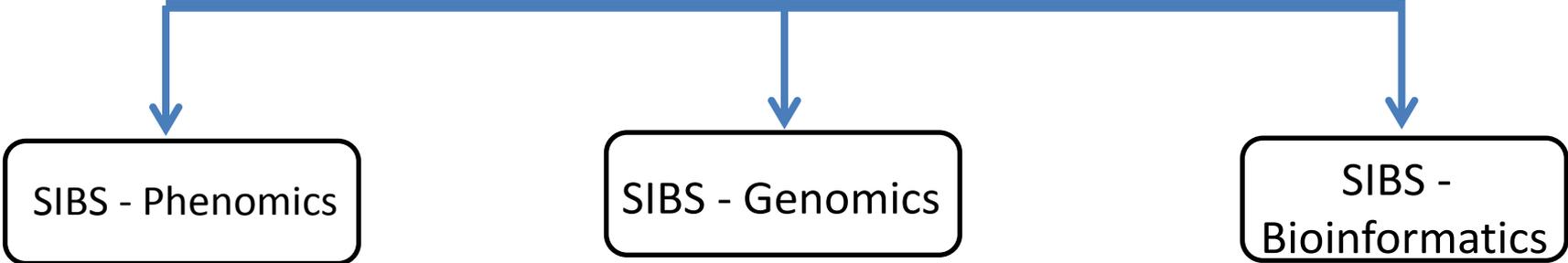
- SIREN is comprised of three interwoven **S**ystematic **I**nvestigation of **B**lacks with **S**troke (**SIBS**) projects geared at a comprehensive investigation of stroke:  
SIBS-Phenomics and Community Engagement  
SIBS-Genomics  
SIBS-Bioinformatics and Genomic Analysis.

# SIREN : Component Projects



# SIREN

3000 case – control pairs



***Accurate phenotyping of cases***

Discovery Phase

*WES  
GWAS  
Candidate gene  
Pathway /Network  
analysis*

Replication Phase

*Validate new SNPs and  
CNVs in REGARDS black  
sub-cohort*

Genomic banking  
for future analysis

*Further analysis with  
emerging techniques*

# SIBS - Phenomics

- To generate *comprehensive and accurate phenomic data on stroke patients and controls* that will assure *reliable phenotyping for the concurrent genomics project (SIBS-Genomics)* focused on evaluating genetic risk factors for stroke (and its subtypes)

# Study Design

- case-control study based on a risk-set sampling frame work
- 3000 cases and 3000 controls

# Sampling Frame

## Cases

- All patients admitted to medical ward, neurology or neurosurgical ward, ICU, Emergency room, or reviewed in an Outpatient Clinic
- study eligibility criteria
- informed consent

## Controls

- Primarily community-based
- Hospital-based controls may be attendants or relatives of another (non-stroke) patient, or
- Patients admitted to the hospital or visiting the hospital for conditions or procedures not related to stroke or TIA.
- Each control is matched for sex, age (+/- 5 years) and ethnicity.
- At least a control (with or without CV risks) for every case recruited.

# Inclusion criteria

## Cases

- Adult with first stroke within 8 days
- CT or MRI is planned within 10 days of symptom onset.

## Controls

- Persons, with no clinical evidence of stroke or MI, with or without cardiovascular risk factors

# Exclusion criteria

## Cases

- Current hospitalization for coronary heart disease
- Unable to provide consent and no surrogate available
- A known previous history of stroke

## Controls

- A known previous history of stroke, or MI
- Unable to provide consent and no surrogate available

To validate stroke –free status in  
our control subjects



1. Have you ever been told by a doctor that you had a stroke?

Yes  No  Don't know

2. Have you ever been told by a doctor that you had a mild stroke or almost had a stroke (TIA)?

Yes  No  Don't know

3. Have you ever had sudden painless weakness on one side of your body?

Yes  No  Don't know

4. Have you ever had sudden numbness or a dead feeling on one side of your body?

Yes  No  Don't know

5. Have you ever had sudden painless loss of vision in one or both eyes?

Yes  No  Don't know

6. Have you ever suddenly lost one half of your vision?

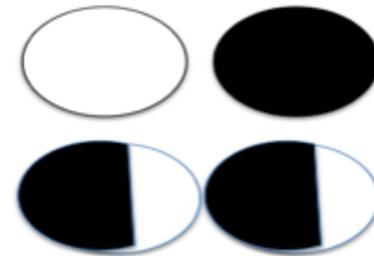
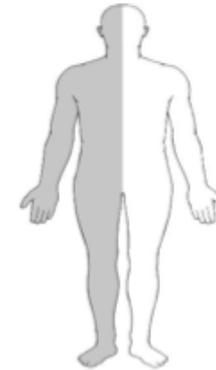
Yes  No  Don't know

7. Have you ever suddenly lost the ability to understand what people are saying?

Yes  No  Don't know

8. Have you ever suddenly lost the ability to express yourself verbally or in writing?

Yes  No  Don't know



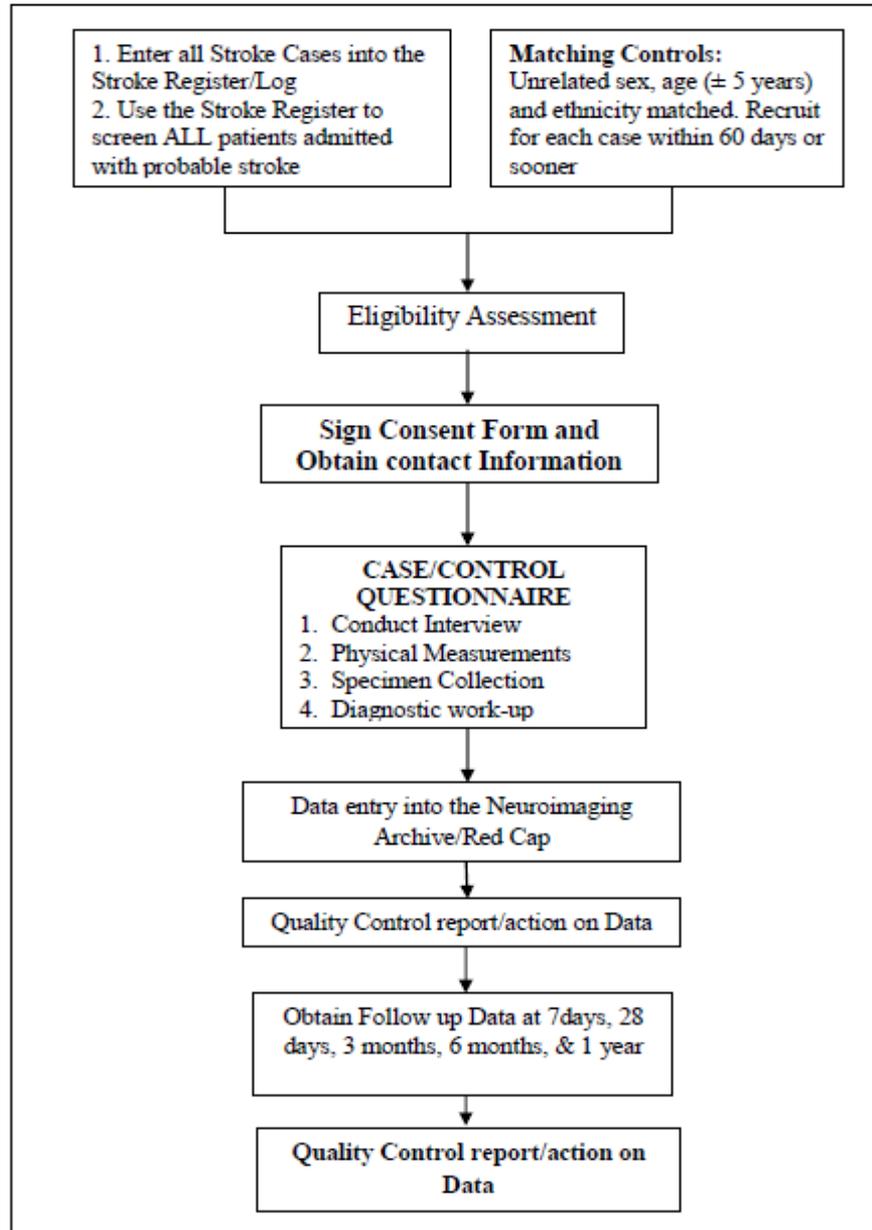
# QVSFS SIREN

- 4 sites: Kumasi, Abeokuta, Ibadan, Zaria/Kano
- Approx. 100 patients each from each site- 50 from general clinic and 50 from neurology/stroke clinic
- Questionnaire were administered by residents in training.
- Confirmation of stroke by a neurologist or specialist at each site AND by a CT scan in a few patients (at least 32).

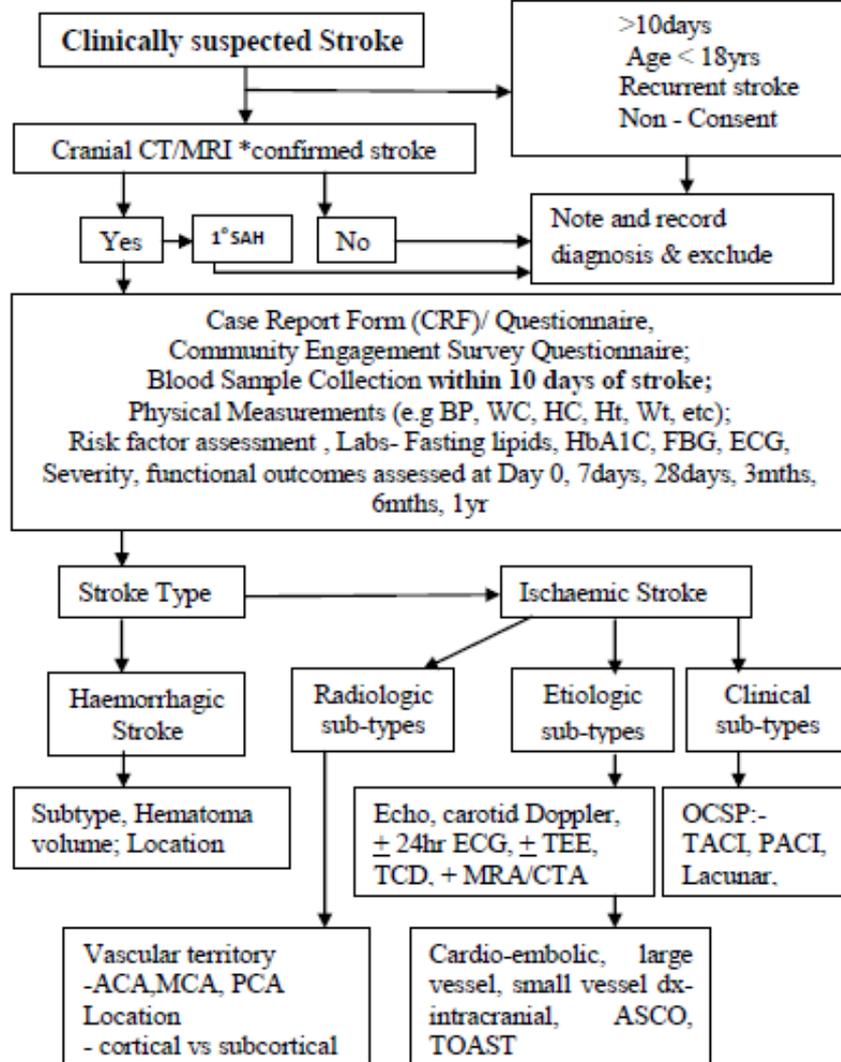
# Performance of the SIREN – adapted 8-Item QVSFS (prelim results, n = 171)

- Sensitivity = 0.94
- Specificity = 0.84
- NPV = 0.94
- PPV = 0.83

# SIREN PROTOCOL



## ALGORITHM FOR INVESTIGATING STROKE PATIENTS



**FOR CONTROLS:** 1. Control CRF; 2. Physical Measurements; 3. FBG; 4. FLP; 5. Blood sample collection immediately after enrolment

- ❖ Blood samples collected from Cases/Controls must be processed **WITHIN TWO HOURS**. Alert the lab before taking samples. If delayed, store in a refrigerator for a maximum of one hour. \* MRI preferred for suspected lacunar or posterior circulation infarct

# Variables for SIBS Phenomics

<b>Variable</b>	<b>Description</b>
<b>Personal and lifestyle factors</b>	Ethnicity, Tobacco use, alcohol use
<b>Socio economic factors</b>	Education, occupation.
<b>Psychosocial factors</b>	Stress, social support, depression,
<b>Medical history</b>	Hypertension, diabetes mellitus, hypercholesterolemia, atrial fibrillation, CVD,
<b>Physical measurements</b>	Blood pressure height, weight, waist and hip circumferences
<b>Neurological assessment</b>	Clinical assessment, neuroimaging, location of lesion, results of diagnostic tests and confirmation of stroke sub-type.

# Variables for SIBS Phenomics

Variable	Description
<b>Stroke Subtype</b>	Based on clinical assessment and Neuroimaging (e.g. CT of brain)- Information on Neurovascular
<b>Blood tests</b>	Lipid profile, fasting blood sugar,
<b>Neuroimaging and other tests</b>	CT or MRI of brain (for all cases), ECG (for all cases), Echocardiography (for all cases of suspected cardioembolic stroke), Carotid Doppler USS (for all cases of ischemic stroke, anterior circulation).
<b>Course in hospital and status at 30 days.</b>	Treatments given, outcomes in hospital, m-Rankin at 30 days

# OCSF

## Classification and natural history of clinically identifiable subtypes of cerebral infarction

JOHN BAMFORD   PETER SANDERCOCK   MARTIN DENNIS  
JOHN BURN   CHARLES WARLOW

We describe the incidence and natural history of four clinically identifiable subgroups of cerebral infarction in a community-based study of 675 patients with first-ever stroke. Of 543 patients with a cerebral infarct, 92 (17%) had large anterior circulation infarcts with both cortical and subcortical involvement (total anterior circulation infarcts, TACI); 185 (34%) had more restricted and predominantly cortical infarcts (partial anterior circulation infarcts, PACI); 129 (24%) had infarcts clearly associated with the vertebrobasilar arterial

groups. Those in the POCI group were at greater risk of a recurrent stroke later in the first year after the index event but had the best chance of a good functional outcome. Despite the small anatomical size of the infarcts in the LACI group, many patients remained substantially handicapped. The findings have important implications for the planning of stroke treatment trials and suggest that various therapies could be directed specifically at the subgroups.

*Lancet* 1991; **337**: 1521–26.

# Trial of ORG 10172 in Acute Stroke Treatment, or TOAST

## Stroke

JOURNAL OF THE AMERICAN HEART ASSOCIATION



### **Epidemiology of Ischemic Stroke Subtypes According to TOAST Criteria: Incidence, Recurrence, and Long-Term Survival in Ischemic Stroke Subtypes: A Population-Based Study**

Peter L. Kolominsky-Rabas, Margarete Weber, Olaf Gefeller, Bernhard Neundoerfer and Peter U. Heuschmann

*Stroke.* 2001;32:2735-2740

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## **New Approach to Stroke Subtyping: The A-S-C-O (Phenotypic) Classification of Stroke**

P. Amarenco<sup>a</sup> J. Bogousslavsky<sup>b</sup> L.R. Caplan<sup>c</sup> G.A. Donnan<sup>d</sup> M.G. Hennerici<sup>e</sup>

# Quality Control Strategies

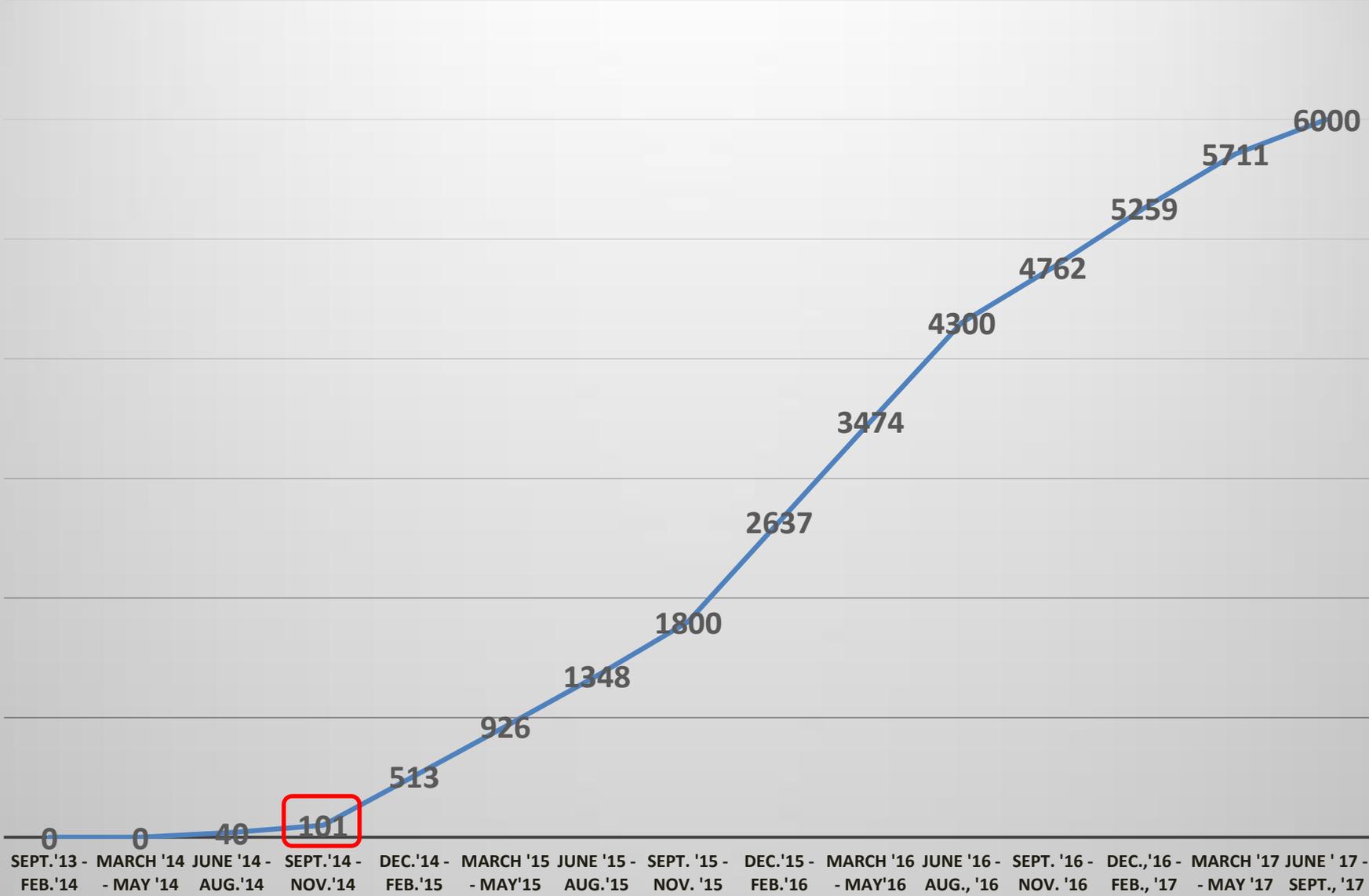
- three levels of adjudication:
- first by the site PI- neurologist/neuroradiologist;
- -secondly by other sites PI- neurologist/neuro-radiologist for verification (peer review)
- thirdly by a ***SIREN stroke phenotyping committee*** comprising: all site PIs, and neuroradiologists (for ambiguous cases)
- and random checks on all classified cases.

# Progress till date

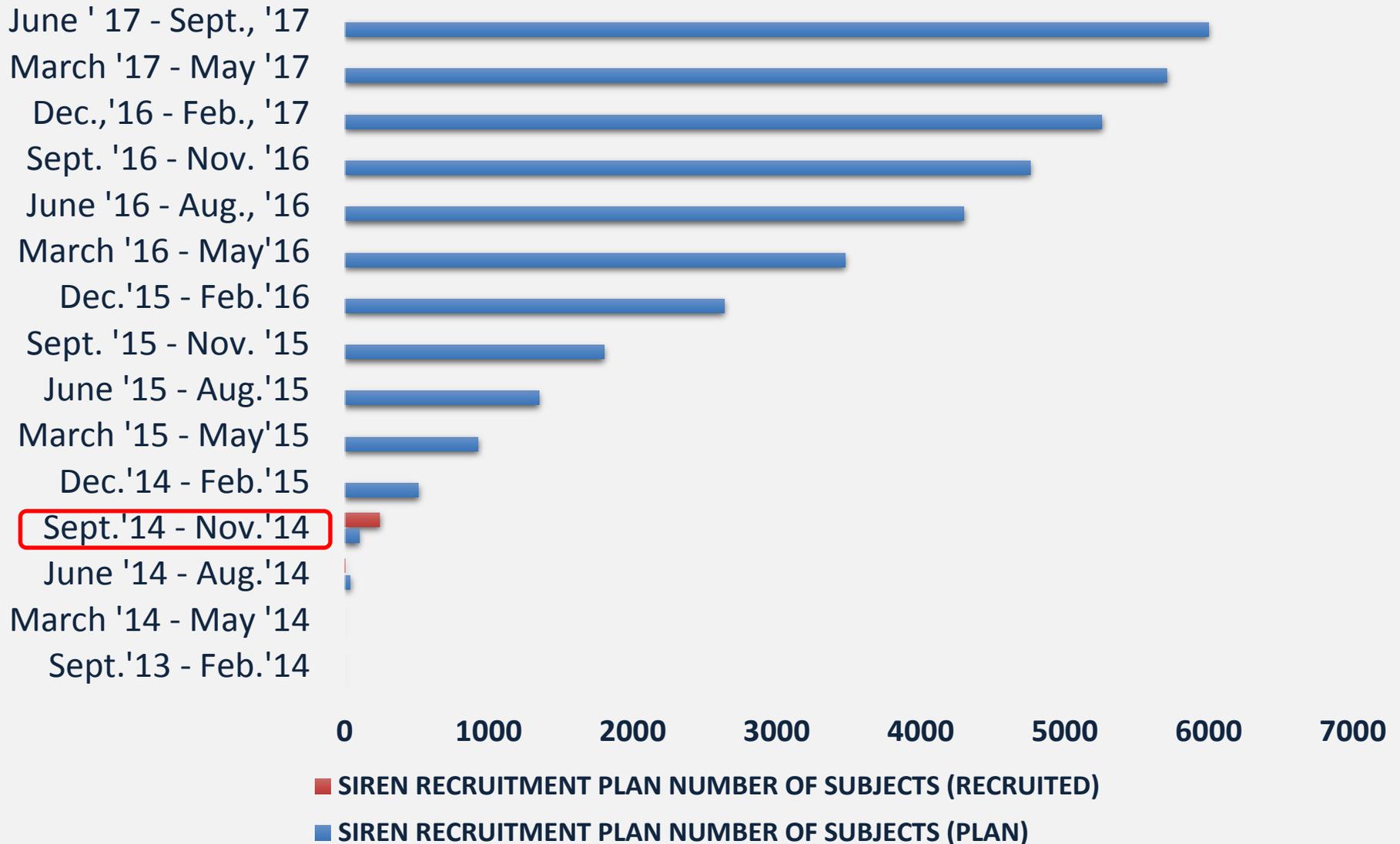
- ✓ Start Date: 20<sup>th</sup> September, 2013.
  
- ✓ Year 1:
  - Ethical approval obtained across all sites
  - international, multidisciplinary project team of 60 professionals set up
  - Study protocols, CRFs ( 1000 variables over 12 months) and SOPs developed
  - procurement of biorepository facilities across sites
  - procurement of sample collection kits
  - training programmes for the team
  - site visits to inspect facilities and harmonize procedures
  
- ✓ Currently in Year 2 of the Project

	SITES	CAB	FGDs	FGD Subjects	SIREN-QVSFS	SIBS PHENOMICS
1	ACCRA	6	4	27	Not Involved	50(33 cases;17 controls)
2	KUMASI	5	4	23	95	48
3	UCH	7	3	16	90	68 (37 cases; 31 controls)
4	BLOSSOM	6	3	17	Not Involved	3
5	FMC	6	3	17	90	21 (18 cases; 3 controls)
6	SACRED HEART	6	3	18	Not Involved	5
7	ZARIA	9	2	12	40	21
8	KANO	7	4	24	45	27 (25 cases 2 controls)
<b>TOTAL</b>		<b>52</b>	<b>26</b>	<b>154</b>	<b>360</b>	<b>243</b>

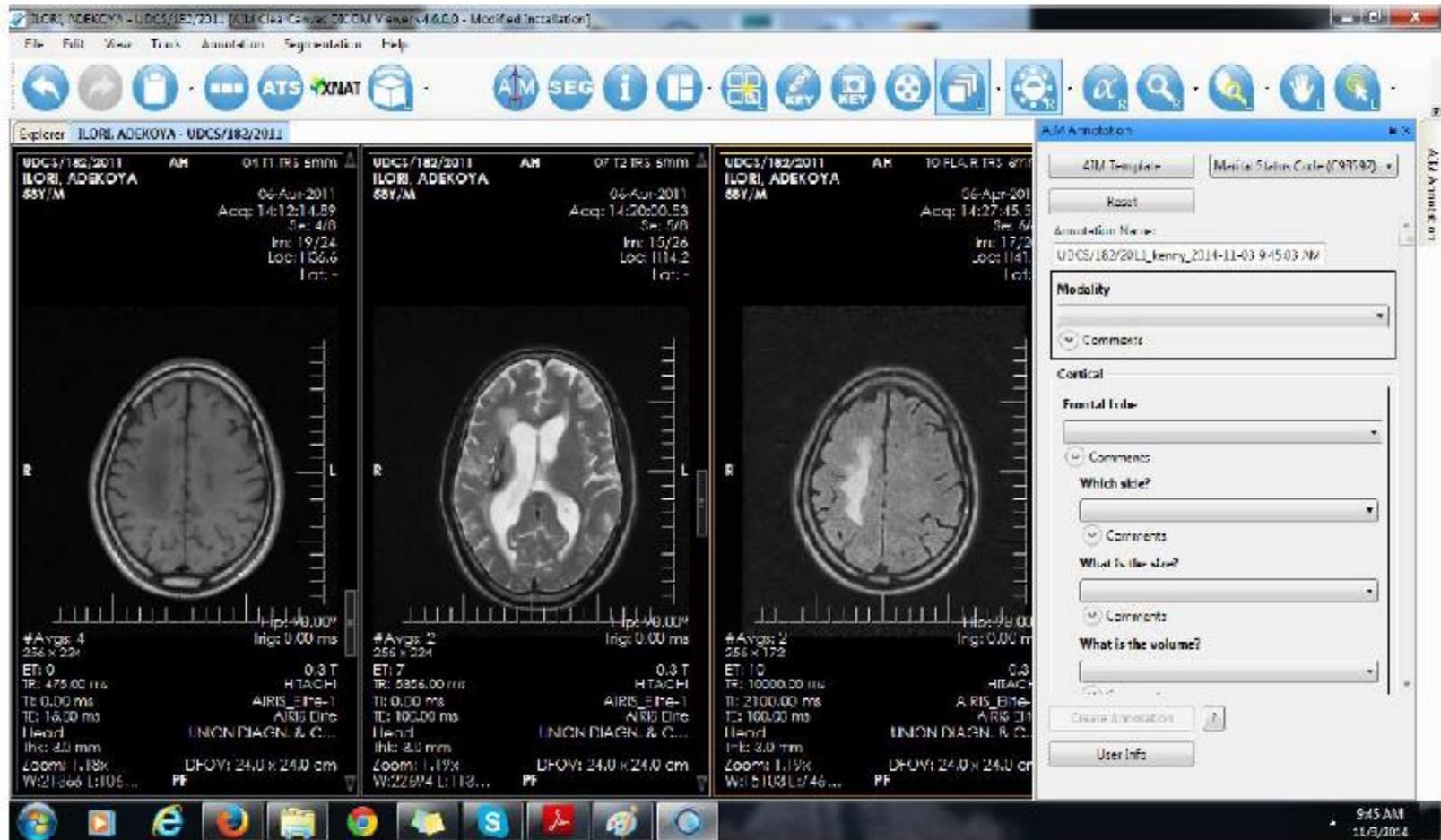
# SIREN : Recruitment Projections



# SIREN: Patient Recruitment



# Neuroimaging archiving with the AIM software



# Centralized electronic data storage

The screenshot displays a web browser window with the URL [http://redcap.emazz.edu/redcap\\_v5.11.1/DataEntry/Index.php?pid=8000&page=accr\\_01en\\_questionnaire](http://redcap.emazz.edu/redcap_v5.11.1/DataEntry/Index.php?pid=8000&page=accr_01en_questionnaire). The page is titled "SIREN Questionnaire" and is part of the REDCap system. The interface includes a sidebar with navigation options like "My Projects", "Data Collection", and "Applications". The main content area shows a "SIREN Questionnaire" section with a "Download PDF of instrument(s)" button and a table of response statistics.

**REDCap™**

Logged in as doctor@emazz.edu | Log out

**My Projects**

- Project Home
- Project Setup
- Project status: **Production**

**Data Collection**

- Manage Survey Participants
- Record Status Dashboard
- ADD / EDIT RECORDS

Data Collection Instruments

- SIREN Questionnaire

**Applications**

- Calendar
- Data export tool
- Field Comment Log
- File Repository
- Graphical Data View & Stats
- Report Builder
- CTRL Website

**Medical University of South Carolina**  
SCTR - Office of Biomedical Informatics Services

**SIREN Questionnaire**

Action: [Download PDF of instrument\(s\)](#)

**SIREN Questionnaire**

You may view an existing record/response by selecting it from one of the drop-down lists below. The records are separated into each drop-down list according to their status for this particular data collection instrument. To create a new record/response, click the button below.

Total records: 2 / Total survey responses: 0 / Last survey response: survey not yet taken

Partial Responses (1)	- select response -
Complete Responses (1)	- select response -
<a href="#">Add new record</a>	

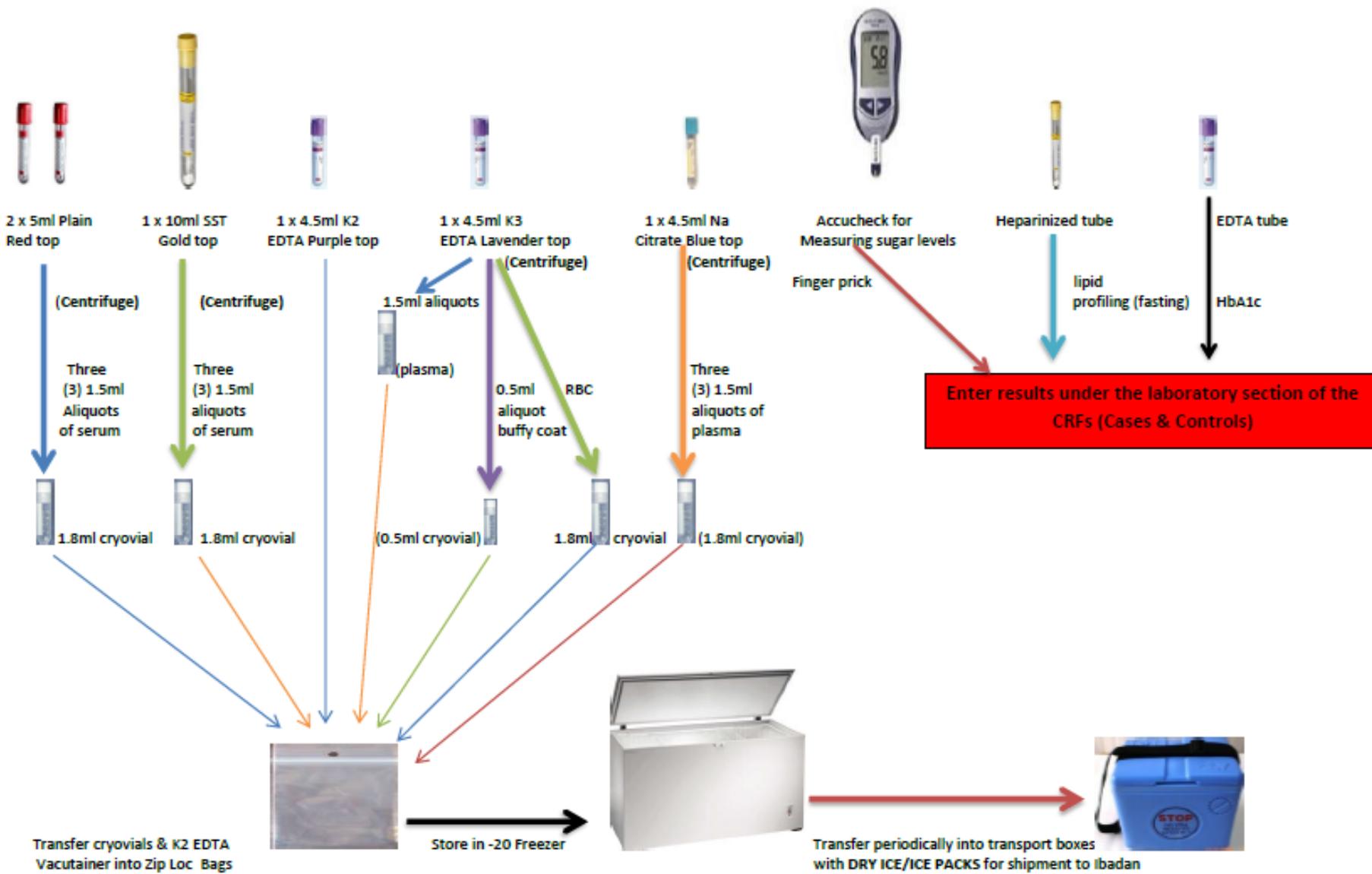
[View instrument record status](#)

9:54 AM 11/3/2011

# SPECIMEN FLOW FOR SIREN SUBJECTS AT BASELINE

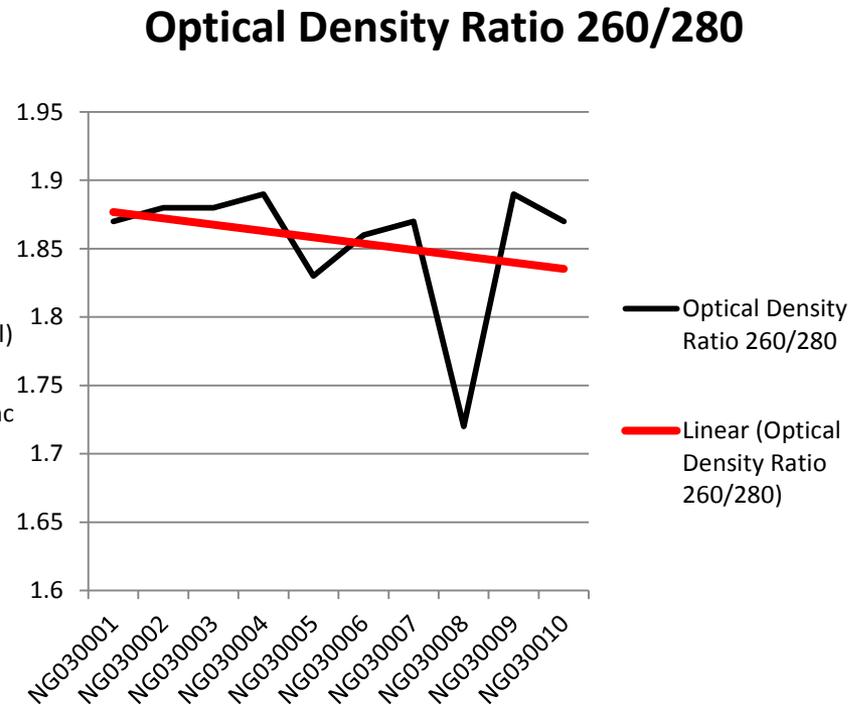
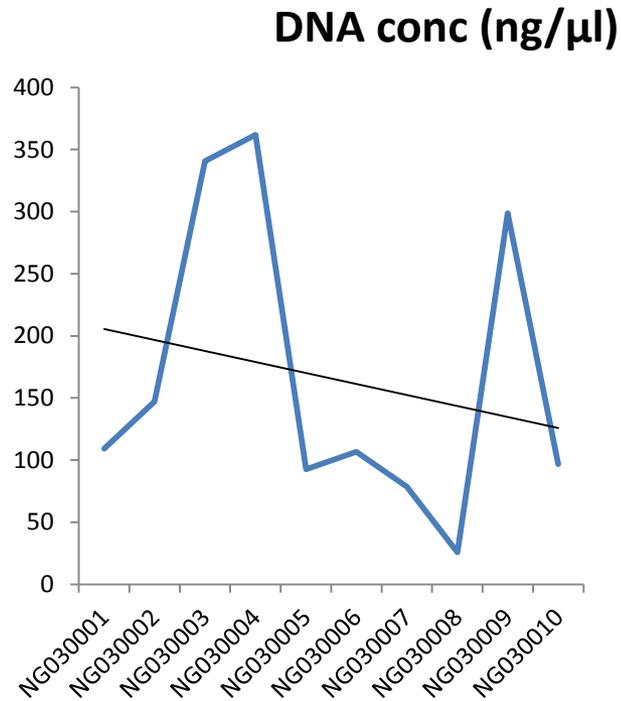
**SOP for Sample processing (Genomic phase)**

**Biochemical Investigations (locally executed)**



• ALERT LABORATORY BEFORE COLLECTING SAMPLES & PROCESS ALL SAMPLES WITHIN 2 HRS OF COLLECTION \* CENTRIFUGATION SHOULD BE DONE AT 3000rpm for 20MINS

# Quantity and Quality of DNA Extract



# Biobanking



- Procurement of biobanking facilities ( $-20^{\circ}\text{C}$  and  $-80^{\circ}\text{C}$ ) with solar - powered inverter back up.
- Staff trained on the use of **freezerworks** and **bar coding** for sample management.
- Daily temperature chart.



# Intensive training programmes for the SIREN Team



- Regular fortnightly SIREN Team meetings by Skype
- Further specialized SIREN WG trainings and meetings (Cardiologists, Neuroradiologists, Sonologists, Laboratory)

# Stroke training programmes for health workers



# Community Engagement



# Community Engagement

- Established Community Advisory Boards across all SIREN performance sites
- Conducted FGDs and structured interviews to evaluate public stroke literacy and KAP of genomic research
- Developed a stroke documentary video for advocacy and educational purposes.

# Challenges

## Challenges

- High cost of investigations
- Power supply and solution found
- Internet connectivity
- Bureaucracies of grant administration
- Political and industrial instability
- Subject retention

## Victories

- Hospital CEOs providing discounts up to 50%
- Inverters including solar powered batteries
- Migrate to better networks
- Continuing engagement with institutional leaders
- Maximize stable periods and remain optimistic
- Keep in touch – mobile phone, CE activities.



“The purpose of life is to contribute in some way to making things better.”

- Robert F. Kennedy

# Conclusion

- SIREN is poised to substantially **enhance our understanding of factors that could be addressed to improve stroke outcomes**, and possibly other vascular disease entities such as coronary artery disease and chronic kidney disease in SSA;
- **discover/explore potentially modifiable genetic pathways to stroke risk that may be common to Black Africans and Black Americans**
- **Making a difference**: taming the burgeoning stroke epidemic in Africa

# Collaborating Institutions

- University of Ibadan, Nigeria
- Medical University of South Carolina, USA
- Department of Epidemiology and Heflin Center for Human Genetics, University of Alabama at Birmingham, USA
- Federal Medical Center, Abeokuta, Nigeria
- Sacred Heart Hospital, Abeokuta, Ibadan, Nigeria
- WFNR-Blossom Medical Center, Ibadan, Nigeria



# Collaborating Institutions

- Aminu Kano University, Kano, Nigeria
- Ahmadu Bello University, Zaria, Nigeria
- University of Ghana, Accra, Ghana
- Kwame Nkrumah University, Kumasi, Ghana
- CPGR
- Institute of Genetic Medicine, Newcastle University, UK
- University College London, UK



# SIREN Investigators

- Mayowa Owolabi - Overall PI
- Bruce Ovbiagele - Overall Co-PI
- Rufus Akinyemi – PI Genomics/Site PI
- Albert Akpalu – PI Phenomics /Site PI
- Kwamena Sagoe- PI Bioinformatics
- Daniel Lackland - co – PI Phenomics
- Mulugeta Gebregziabher - Biostatistician
- Oyedunni Arulogun- Community Engagement
- Carolyn Jenkins – Community Engagement
- Fred Stephen Sarfo- Site PI
- Reginald Obiako – Site PI
- Lukman Owolabi – Site PI

# SIREN Support Team

- Program Manager
- Research Coordinators
- Research Assistants
- Community Engagement Coordinators
- Neuroradiologists/Sonologists
- Cardiologists
- Resident Doctors
- Medical Laboratory Scientists

# FUNDERS

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