STUDY PROTOCOL

A placebo controlled clinical trial investigating the safety and immunogenicity of GBS6 in pregnant women with and without human immunodeficiency virus (HIV) infection and their infants

Sponsor:

St George's, University of London

Cranmer Terrace SW17 0RE

FUNDING SOURCE:

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PREPARE

REDUCING NEONATAL, INFANT AND MATERNAL GBS IN AFRICA

GCP Compliance: The study will be conducted in compliance with ICH-GCP and all applicable regulatory body requirements.

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Protocol Version 5.0, Dated 01/02/2023

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2. SIGNATURE PAGE AND STATEMENT

The Chief Investigator (CI), Principal Investigator (PI) and the Sponsor Representative have discussed this protocol version. The investigators agree to perform the investigations and to abide by this protocol except where departures from it are mutually agreed in writing.
The Investigators agree to conduct the trial in compliance with the approved protocol and all data will be handled in accordance with the Uganda Data Protection Act 2019 and the UNCST guidelines.

In addition it will also be in compliance with the approved protocol GCP, the UK Data Protection Act (1998), the St George's, University of London Information Governance Policy (or other local equivalent), the Research Governance Framework (2005 2nd edition) and the Sponsor's SOPs, as appropriate.

By our signatures below, we hereby confirm that we will conduct the study described in this protocol in compliance with ICH/GCP and the version of such protocol agreed to by the applicable local and international regulatory authorities approved by the study Institutional Review Board and Ethical Committees.

Chief Investigator (Dr Kirsty Le Doare)

Principal Investigator (Dr Musa Sekikubo)

Signature _____

Date

Please note that study responsibilities are documented in the Trial Master and Investigator Site Files.

A placebo controlled clinical trial investigating the safety and immunogenicity of GBS6 in pregnant women with and without human immunodeficiency virus (HIV) infection and their infants

CONTENTS

2. List of abbreviations

AE	Adverse Event
ART	Antiretroviral Therapy
CD4	Cluster of Differentiation 4
CPS	Capsular Polysaccharide
CRF	Case Report Form
EDP	Exposure During Pregnancy
ELISA	Enzyme-Linked Immunosorbent Assay
EPI	Expanded Program on Immunization
GBS	Group B Streptococcus
GBS6	Group B streptococcus 6-valent polysaccharide conjugate vaccine
GCP	Good Clinical Practice
GMC	Geometric Mean Concentration
HCV	Hepatitis C virus
HELLP	Haemolysis, elevated liver enzymes and low platelet count
HIV	Human Immunodeficiency Virus
HSV	Herpes simplex virus
IAP	Intrapartum antibiotic prophylaxis
ICD	Informed consent document
ICF	Informed Consent Form
ICH	International council for Harmonisation
ID	Identification
IgG	Immunoglobulin G
INR	International normalized ratio
IP	Investigational product
IRB	Institutional review board
IRC	Internal review committee
IWR	Interactive Web-based response

LFT	Liver function test
LMIC	Low- and Middle-Income Countries
LMP	Last menstrual period
LSLV	Last participant last visit
MAE	Medically attended adverse event
mITT	Modified intent to treat
N/a	Not applicable
OPA	Opsonophagocytic activity
OPkA	Opsonophagocytic killing assay
PDA	Personal digital assistant
PI	Principal Investigator
RCDC	Reverse cumulative distribution curve
REC	Research Ethics Committee
SAE	Serious Adverse Event
SAGE	Strategic Advisory Group of experts
SAP	Statistical analysis plan
SOP	Standard Operating Procedure
SRM	Study reference manual
SRSD	Single reference safety document
TBili	Total Bilirubin
ULN	Upper limit of normal
WG	Week's Gestation

3. Protocol synopsis

Official title:	**A placebo controlled clinical trial investigating the safety and immunogenicity of GBS6 in pregnant women with and without human immunodeficiency virus (HIV) infection and their infants**
Brief title /Acronym:	PREPARE: WP4
Sponsor reference number:	2020.0317
Public database trial ID:	The study will be registered on clinicaltrials.gov once the protocol is approved
Hypothesis	We hypothesise that the safety profile and tolerability of a hexavalent Group B Streptococcal vaccine is the same in women living with HIV and women who do not have HIV.
Primary Objectives	1. To describe the safety and tolerability of GBS6 when administered at ≥ 27 0/7 to ≤ 35 6/7 weeks' gestation to pregnant women, with and without HIV, aged ≥ 18 to ≤ 40 years of age and their infants. 2. To assess the safety of GBS6 in infants born to HIV positive and negative women who were vaccinated during pregnancy.
Secondary Objectives	1. To describe the immunogenicity of GBS6 when administered to pregnant women with and without HIV. 2. To describe GBS-specific antibody levels in infants born to women vaccinated with GBS6 during pregnancy. 3. To assess placental transfer of GBS-specific antibodies from pregnant women vaccinated with GBS6 to their infants.

Exploratory Objectives	1. To describe the persistence of serotype-specific antibody responses to the GBS6 vaccine up to 12 months following delivery. 2. To characterise GBS colonisation status in maternal participants 3. To describe the immune responses in breastmilk in women with and without HIV vaccinated with GBS6. 4. To describe the immune responses to Expanded Programme on Immunisation (EPI) administered to HIV-exposed and unexposed infant participants born to maternal participants vaccinated with GBS6. 5. To characterise GBS colonisation status in infant participants at birth, 6 weeks and 18 weeks of age. 6. To explore GBS6 antibody levels from dried blood spots in infant participants at birth.
Study design	Randomised, placebo controlled, double-blind, parallel group trial. Subjects will be a randomized 1:1 to GBS6/placebo stratified by baseline HIV status: 1. HIV-uninfected women, placebo (saline) in pregnancy; 2. HIV-uninfected women, GBS6 in pregnancy; 3. HIV-infected women, placebo (saline) in pregnancy; 4. HIV-infected women, GBS6 in pregnancy.
Eligibility criteria:	**Inclusion criteria for Maternal participants** 1. Age ≥ 18 to ≤ 40 years of age, inclusive at day of signing the

	ICF. 2. Pregnant at ≥ 27 0/7 to ≤35 6/7 gestation on the day of planned vaccination, verified by ultrasound scan (U/S). 3. Low risk, singleton pregnancy, as assessed by the study physician based on ultrasound scan and previous obstetric history. 4. Documented negative HBV surface antigen, HCV antibody, and syphilis tests at screening. 5. Normal full blood count (CBC), renal and liver function tests at screening. 6. Documented HIV test during pregnancy undertaken as per the national guidelines. 7. If HIV infected pregnant women, stable on ART for at least 2 months prior to study start with an undetectable viral load (VL) 8. Determined by medical history, physical examination, screening laboratory assessment, and clinical judgment to be appropriate for inclusion in the study. 9. Receiving prenatal standard of care including HIV care if applicable at the clinics/physician offices/hospital network affiliated with the clinical study site. 10. Willing to give birth at Kawempe Specialised National Referral Hospital, Kawaala or Komamboga Health Centre III or Wakiso or Kisenyi Health center IV, Uganda. 11. Willing and able to participate for the duration of the study visits and follow-up until 12-months post-delivery. 12. Willing and able to be contacted by telephone for the full

	duration of the study, and to give informed consent for their infant participant to participate in the study. **Inclusion criteria for Infants** 1. Parent(s) willing and able to comply with scheduled visits, investigational plan, laboratory tests, and other study procedures.
	Exclusion criteria for Maternal Participants Any of the following: 1. Investigator site staff members directly involved in the conduct of the study and their family members, site staff members otherwise supervised by the investigator, or participants who are Pfizer employees, including their family members, directly involved in the conduct of the study. 2. Participants whose unborn baby have been fathered by investigational site staff members directly involved in the conduct of the study or their family members, site staff members otherwise supervised by the investigator, or Pfizer employees directly involved in the conduct of the study. 3. Participation in other studies involving investigational drug(s), vaccines, or medical devices within 28 days prior to study entry and/or during study participation. 4. Previous vaccination with any licensed or investigational GBS vaccine. 5. History of severe adverse reaction associated with a vaccine and/or severe allergic reaction (e.g., anaphylaxis) to any component of the investigational product.

	6. History of microbiologically proven invasive disease caused by GBS, or history of an infant with GBS disease. 7. Current alcohol abuse or illicit drug use. 8. Body mass index (BMI) of ≥40 kg/m^2 at the time of the screening visit. 9. Clinical history of primary genital herpes simplex virus (HSV) infection during the current pregnancy. 10. A prior history of or current pregnancy complications or abnormalities that will increase the risk associated with the participant's participation in, and completion of, the study, including but not limited to the following : a) Gestational hypertension or preeclampsia or eclampsia b) Placental abnormality c) Polyhydramnios or oligohydramnios d) Significant bleeding or blood clotting disorder e) Gestational diabetes f) Any signs of premature labour with the current pregnancy g) Prior late stillbirth (defined as loss of pregnancy at any time after 28 weeks gestation) or neonatal death (defined as death of an infant within the first 28 days of life), prior low birth weight baby (defined as infant <2500 g) or premature delivery (defined as delivery before 37 0/7 weeks gestation), prior history of at least 3 miscarriages, prior pregnancies numbering greater than 5, or previous infant with a known or suspected genetic disorder or major congenital anomaly. h) Confirmed GBS bacteriuria during the current pregnancy

	11. Major illness of the mother (outside of HIV serostatus) or conditions of the foetus that, in the investigator's judgment, will substantially increase the risk associated with the participant's participation in, and completion of, the study or could preclude the evaluation of the participant's response, including but not limited to the following: a) hypertension requiring treatment b) heart disease c) lung disease d) neurological disorders including a history of epilepsy or recurrent afebrile seizures e) kidney disease f) liver disease g) haematological disorders (including sickle cell disease) h) severe anaemia (less than 7.0g/dL) i) significant bleeding or blood clotting disorder j) endocrine disorders including known diabetes mellitus 12. Participants with known or suspected immunodeficiency (outside of HIV positive serostatus). 13. Participants who receive treatment with immunosuppressive therapy including cytotoxic agents or systemic corticosteroids, e.g., for cancer or an autoimmune disease, or planned receipt through the postvaccination blood draw. Inhaled/nebulised, intraarticular, intra-bursal, or topical (skin or eyes) corticosteroids are permitted. 14. Receipt of blood/plasma products or immunoglobulin, from

	60 days before investigational product administration, or planned receipt through delivery. 15. Known to be Rhesus Negative 16. Psychiatric condition including recent (within the last year) or active suicidal ideation or behaviour or laboratory abnormalities that may increase the risk associated with study participation or investigational product administration or may interfere with the interpretation of study results and, in the judgment of the investigator, would make the participant inappropriate for entry into this study. 17. Deprived of freedom by an administrative or court order, or in an emergency setting, or hospitalised involuntarily.
Anticipated start date	October 2022
Anticipated end date	September 2024
Target number of participants	Total = 300; 75 in each of the four groups listed above
Primary Safety Endpoints (Maternal Participants)	1. Occurrence of solicited local reactions within 7 days following administration of investigational product (pain at the injection site, redness, and swelling). 2. Occurrence of solicited systemic events within 7 days following administration of investigational product (fever, nausea/vomiting, diarrhoea, headache, fatigue/tiredness, muscle pain, and joint pain). 3. Occurrence of solicited and unsolicited adverse events through 1 month after administration of investigational product. 4. Occurrence of SAEs, MAEs, and obstetric complications

	(peripartum, intrapartum, and postpartum) throughout the study (Visit 1 through the 12month post-delivery study visit) and any unsolicited events leading to study withdrawal.
Primary Safety Endpoints (Infant Participants)	1. Occurrence of unsolicited adverse events from birth to 6 weeks of age 2. Occurrence of SAEs, AEs of special interest (major congenital anomalies, developmental delay, and suspected or confirmed GBS infection), and MAEs through 12 months of age and any unsolicited events leading to study withdrawal.
Secondary Immunologic Endpoints (Maternal Participants)	1. GBS serotype-specific IgG antibody titres measured at baseline, 2 weeks, 1 month after vaccination, at delivery and 6 weeks after delivery in HIV positive and HIV negative women. 2. GBS serotype-specific OPA titres measured at baseline, and at delivery in HIV positive and HIV negative women.
Secondary Immunologic Endpoints (Infant Participants)	1. GBS serotype-specific IgG antibody titres in HIV-exposed and unexposed infant participants measured at birth, 18 weeks and 12 months of life. 2. GBS serotype-specific OPA titres in HIV-exposed and unexposed infant participants measured at 18 weeks of life. 3. Placental transfer ratio of GBS-specific antibodies in HIV-exposed and unexposed pregnancies.
Exploratory Endpoints (Maternal	1. Fold increase in GBS serotype-specific IgG antibody titres over baseline measured before vaccination through

participants)	12 months after delivery in HIV positive and HIV negative women. 2. Serotype-specific GBS positive vaginal and/or rectal culture(s) before vaccination, at delivery, and 6 weeks after delivery in HIV positive and HIV negative women. 3. GBS serotype-specific IgG and IgA antibody titres in breast milk following vaccination of women living with HIV and their unexposed counterparts in colostrum (within 72 hours of delivery) and breast milk at 6 and 18 weeks after delivery.
Exploratory Endpoints (Infant participants	1. IgG antibody titres to vaccines included in the extended programme of vaccination administered to HIV-exposed and unexposed infant participants as part of at 18 weeks and 12 months of age. 2. Serotype-specific GBS positive nasal/rectal cultures at delivery, 6 weeks and 18 weeks after delivery in infant participants. 3. GBS serotype-specific IgG antibody titres measured from dried blood spots in infant participants at birth.
Sources of funding	EDCTP, RIA2018V-2304
Sponsor	St George's, University of London

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4. Background

Group B Streptococcus (GBS) is a leading cause of neonatal infection (including pneumonia, sepsis and meningitis) in Europe, and increasingly recognised as a significant cause of neonatal infection in Sub-Saharan Africa [1]; over 319,000 infant cases are estimated to occur globally each year [2]. GBS also accounts for 33,000 cases of disease in pregnant or post-partum women, 57,000 stillbirths and 90,000 infant deaths [3–5] - more than the total number of deaths from mother-to child transmission of HIV and more than the combined neonatal deaths from tetanus and pertussis [1], for which maternal vaccines are currently available. An effective GBS vaccine could reduce disease in the mother, foetus and infant and is a global priority. It is estimated that an effective GBS maternal vaccine (>80% efficacy) with high (90%) global coverage could prevent 231,000 infant and maternal GBS cases, 41,000 stillbirths and 66,000 infant deaths globally each year [1]. However, several important obstacles exist before any such vaccine could be implemented.

The epidemiological data upon which to estimate the GBS disease burden and potential critical impact of vaccination is lacking in many African countries[6]. Indeed, the causes of neonatal disease and deaths in general, are not well established in this setting; this is an important knowledge gap because these countries have high stillbirth, neonatal and infant death rates and a substantial proportion of these are likely to be due to infections [7].

4.1. GBS in Uganda

Despite representing only 13% of the world's population, Africa has the highest burden of GBS disease, with 54% of estimated cases and 65% of stillbirths and infant deaths and the highest incidence of invasive GBS disease in infants at 1.12/1000 livebirths [2]. Widespread applicability of the vaccine to prevent GBS disease in this setting is further complicated by the high burden of HIV infection. There have been no large studies of GBS disease in

Uganda, except for a study of 290 febrile infants between 0-28 days of life at Mulago hospital in 2002, of which 55 infants had a blood culture obtained and 7 (13%) were found to have GBS disease [8]. We have recently undertaken a longitudinal study of 25,000 livebirths in Kampala, Uganda and found a disease incidence of 1.4 per 1000 livebirths [9].

4.2. Antenatal and infant care in Uganda

Recent data from Uganda show a maternal mortality of 343 per 100 000 live births, neonatal mortality of 19 deaths per 1000 live births and under-five mortality rate of 55 per 1000 live births [10]. In Uganda only 57% of women receive the WHO recommended minimum four antenatal clinic visits although at least 75% receive two doses of tetanus vaccination in pregnancy and more than 95% of women receive antiretroviral therapy [10]. At present in Uganda, there is no policy of routine GBS screening of pregnant women attending antenatal care and therefore little use of intrapartum antibiotic prophylaxis.

4.3. Protecting infants through maternal vaccination

Protecting mothers and their infants during pregnancy and the first few months of life is challenging. However, young infant protection is provided by placental transfer of maternally derived IgG antibody[11]. This protection can be further enhanced through vaccination in pregnancy and several vaccines are now routine [12]. Rates of neonatal tetanus have declined dramatically in many African countries since the introduction of maternal tetanus toxoid vaccination [13]. Immunisation during pregnancy has also been shown to decrease the infant's risk of pertussis infection[14]. Different factors might affect the magnitude of the trans-placental transfer of IgG to the newborn including the mothers' health status, the concentration of total and vaccine-specific IgG in maternal sera, the integrity of the placenta, the type and timing of vaccine administration to the pregnant women during pregnancy [14]. Of particular concern is maternal HIV infection - there are no data on the immunogenicity of GBS vaccines in pregnancy in HIV-infected women.

4.4. The burden of HIV infection in pregnancy

Globally, almost 1,000 young women are newly infected with HIV daily. In 2013, 1.5 million HIV-infected women worldwide gave birth and of these approximately 60% had access to antiretroviral therapy (ART) [15]. In the era of widespread ART, the vast majority of infants born to HIV infected women are exposed to HIV but uninfected (HEU) leading to a dramatic increase in the absolute number of HEU infants. HEU infants are exposed in utero to HIV particles that might have an effect on their immunologic functions [16]. This immune dysfunction is thought to place the vulnerable HEU at increased risk for infectious diseases mortality and morbidity [16]. HEU infants appear to be at greater risk of GBS disease than their HIV unexposed peers [17]. This could be partially due to the reduced transfer of antibodies across the placenta resulting in lower infant antibody concentrations that wane rapidly, a phenomenon noted in HEU infants for several vaccine-preventable diseases (e.g. *Haemophilus influenzae type B*, acellular pertussis, tetanus) [18].Uganda is a country with a high pregnancy rate (189 per 1000 women age 15-44), infant mortality (38/1000 livebirths) and high HIV rate in pregnant women (7%) [10].

4.5. Current status of GBS vaccine

Several vaccines for use in pregnancy are now in clinical trials. The most advanced vaccine candidates are hexavalent vaccines including serotypes Ia, Ib, II, III, IV, and V, which are now in phase II trials [19]. Immunogenicity and safety of these candidates has been demonstrated in non- pregnant women [20] and in HIV-uninfected women in South Africa(ClinicalTrials.gov Identifier: NCT03765073). Protein-based vaccines are also in phase II trials [21].

4.6. Alternatives to Phase III efficacy trials

To progress a GBS vaccine to phase III trials would likely require vaccination of over 100,000 pregnant women if the trial endpoint is invasive neonatal and infant GBS disease [22]. Given the complexity, size and costs associated with a study of this size, it is generally agreed that indirect evidence (correlates) of protection (CoP), based on immunologic data from vaccine and sero-epidemiological studies, opsonophagocytic assays and supported by animal models, could be pivotal for vaccine licensure, with effectiveness subsequently confirmed in post-licensure evaluations [23]. This was the approach taken for licensure of childhood vaccines such as those for *Neisseria meningitidis* [24]. However, establishing a valid correlate of protection for GBS requires further work [25].

4.7. Developing a sero-correlate of protection against GBS

Although maternal GBS colonisation is common, very few colonised infants (1-2%) subsequently develop invasive GBS disease [26]. Studies indicate that high concentrations of naturally occurring capsular serotype-specific maternal IgG antibody correlate with a reduced risk of disease in neonates [25]. The association between serotype-specific capsular polysaccharide (CPS) antibody levels and GBS in newborns was initially characterised in 1976 by Baker and colleagues [27]. In all subsequent studies lower serotype-specific CPS antibodies were found in infants with early onset (EO) and late onset (LO) GBS compared with controls. In a meta-analysis comparing the proportions of cases and controls with CPS antibody levels ≥2 ug/ml, the odds of GBS was 6.56 (95% CI: 2.10–20.55) and 2.38 (95% CI: 1.20–4.70) times greater in infants whose mothers had antibody levels <2 ug/ml for serotypes III and Ia, respectively [28]. A threshold of 1 ug/ml has also recently been proposed as a correlate for protection for serotypes Ia and III [29]. Thresholds are much higher in other large studies [30] including a study from South Africa [31]. Interpretation of these studies is difficult due to differences in endpoints (EO vs LO), assays and statistical analyses, as well as the lack of reference sera.

Thus, a standardised approach to establish antibody concentration and function and its role in reducing neonatal disease is vital in achieving licensure of any future vaccines [32].

4.8. Group B streptococcus hexavalent polysaccharide conjugate vaccine [GBS6]

Pfizer is developing a hexavalent capsular polysaccharide (CPS) conjugate vaccine (group B streptococcus hexavalent polysaccharide conjugate vaccine [GBS6]) aimed at the prevention of group B streptococcal disease due to 6 serotypes (Ia, Ib, II, III, IV, and V) in young infants by active immunisation of pregnant women[19]. GBS6 has been developed based on Pfizer's historical experience with licensed and investigational polysaccharide conjugate vaccines, and published/public data with other investigational GBS CPS conjugate vaccines that have been evaluated in clinical trials, including a trivalent (Ia, Ib, and III) GBS CPS–cross-reactive material 197 (CRM_{197}) conjugate vaccine in pregnant women [33]. A phase 1/2, placebo-controlled, observer-blinded, dose-escalation trial, done at four clinical research centres in the USA in healthy, non-pregnant adults aged 18–49 years showed that the vaccine was well tolerated and elicited robust immune responses for all dose levels and formulations that persisted 6 months after vaccination [20].

This Phase 2, randomised, placebo controlled, double blinded study will be the first evaluation of the investigational GBS6 in HIV-infected pregnant women. This study will enroll pregnant women with and without HIV to receive the GBS6 in order to provide an expanded safety and immunogenicity data set (for both pregnant women and their infants) and to support progression of the development of this vaccine.

4.9. Investigational Product

The investigational products are GBS6 and placebo (saline control). The GBS6 dose will be GBS6 20mcg without AlPO4 (equivalent to 240 mcg/mL) 0.5mL dose or 20 mcg CPS/sero-type).

5. Research Questions

5.1 Hypothesis

We hypothesise that the safety profile and tolerability of a hexavalent Group B Streptococcal vaccine is the same in women living with HIV and women who do not have HIV.

5.2. Primary, secondary and exploratory objectives

A. Primary Objectives

- A1. Primary Objective 1: To describe the safety and tolerability of GBS6 when administered at ≥ 27 0/7 to ≤ 35 6/7 weeks' gestation to pregnant women, with and without HIV, aged ≥ 18 to ≤ 40 years of age and their infants.
- A2. Primary Objective 2: To assess the safety of GBS6 in infants born to HIV positive and negative women who were vaccinated during pregnancy.

B. Secondary Objectives

- B1. Secondary Objective 1: To describe the immunogenicity of GBS6 when administered to pregnant women with and without HIV.
- B2. Secondary Objective 2: To describe GBS-specific antibody levels in infants born to women vaccinated with GBS6 during pregnancy.
- B3. Secondary Objective 3: To assess placental transfer of GBS-specific antibodies from pregnant women vaccinated with GBS6 to their infants.

C. Exploratory objectives

- C1. To describe the persistence of serotype-specific antibody responses to the GBS6 vaccine up to 12 months following delivery.
- C2. Exploratory Objective 2: To characterise GBS colonisation status in maternal participants

• C3. Exploratory Objective 3: To describe the immune responses in breast milk in women with and without HIV vaccinated with GBS6.

• C4. Exploratory Objective 4: To describe the immune responses to Expanded Programme on Immunisation (EPI) administered to HIV-exposed and unexposed infant participants born to maternal participants vaccinated with GBS6.

• C5. Exploratory Objective 5: To characterise GBS colonisation status in infant participants at birth, 6 weeks and 18 weeks of age.

• C6. Exploratory Objective 6: To explore GBS6 antibody levels from dried blood spots in infant participants at birth.

5.2 Primary, secondary and exploratory endpoints

Primary endpoints for primary objectives A1 and A2:

• Maternal primary endpoint 1: Occurrence of solicited local reactions within 7 days following administration of investigational product (pain at the injection site, redness, and swelling).

• Maternal primary endpoint 2: Occurrence of solicited systemic events within 7 days following administration of investigational product (fever, nausea/vomiting, diarrhoea, headache, fatigue/tiredness, muscle pain, and joint pain).

• Maternal primary endpoint 3: Occurrence of solicited and unsolicited adverse events through 1 month after administration of investigational product.

• Maternal primary endpoint 4: Occurrence of SAEs, MAEs, and obstetric complications (peripartum, intrapartum, and postpartum) throughout the study (Visit 1 through the 12month post-delivery study visit) and any unsolicited events leading to study withdrawal.

• Infant primary endpoint 1: Occurrence of unsolicited adverse events from birth to 6 weeks of age

• Infant primary endpoint 2: Occurrence of SAEs, AEs of special interest (major congenital anomalies, developmental delay, and suspected or confirmed GBS infection), and MAEs through 12 months of age and any unsolicited events leading to study withdrawal.

Secondary endpoints for secondary objectives B1, B2, B3:

• Maternal secondary endpoint 1: GBS serotype- specific IgG antibody titres measured at baseline, 2 weeks, 1 month after vaccination, at delivery and 6 weeks after delivery in HIV positive and HIV negative women.

• Maternal secondary endpoint 2: GBS serotype specific IgG titres measured at baseline, and at delivery in HIV positive and HIV negative women.

• Infant secondary endpoint 1: GBS serotype specific IgG antibody titres in HIV-exposed and unexposed infant participants measured at birth, 18 weeks and 12 months of life.

• Infant secondary endpoint 2: GBS serotype specific IgG titres in HIV-exposed and unexposed infant participants measured at 18 weeks of life.

• Infant secondary endpoint 3: Placental transfer ratio of GBS-specific antibodies in HIV-exposed and unexposed pregnancies.

Exploratory endpoints for exploratory objectives C1 to C6:

• Maternal exploratory endpoint 1: Fold increase in GBS serotype specific IgG antibody titres over baseline measured before vaccination through 12 months after delivery in HIV positive and HIV negative women.

• Maternal exploratory endpoint 2: Serotype specific GBS positive vaginal and/or rectal culture(s) before vaccination, at delivery, and 6 weeks after delivery in HIV positive and HIV negative women

• Maternal exploratory endpoint 3: GBS serotype specific IgG and IgA antibody titres in breast milk following vaccination of women living with HIV and their unexposed counterparts in colostrum (within 72 hours of delivery) and breast milk at 6 and 18 weeks after delivery

• Infant exploratory endpoint 1: IgG antibody titres to vaccines included in the extended programme of vaccination administered to HIV-exposed and unexposed infant participants as part of at 18 weeks and 12 months of age.

• Infant exploratory endpoint 2: Serotype specific GBS positive nasal/rectal cultures at delivery, 6 weeks and 18 weeks after delivery in infant participants.

• Infant exploratory endpoint 3 GBS serotype specific IgG antibody titres measured from dried blood spots in infant participants at birth.

6. Statistical design

6.1 Sample size

This is a Phase 2 randomised, placebo controlled, double-blinded study to assess safety, tolerability, and immunogenicity of GBS6 in pregnant HIV positive and HIV negative women and their infant participants. It will be the first evaluation of the investigational GBS6 vaccine in HIV-infected pregnant women. This study will enroll pregnant women with and without HIV to receive the GBS6 in order to provide an expanded safety and immunogenicity data set (for both pregnant women and their infants) and to support progression of the development of this vaccine. As such, the statistical analyses are largely descriptive and the sample size is chosen based on what is achievable at the site. Additionally, and consistent with the clinical phase of the study (II), the primary outcome is based on safety.

Regarding safety, for common pregnancy outcomes such as prematurity, this sample size of 300 in total would provide 80% power (5% alpha) to detect an increase in prematurity outcomes from a background rate of 10% in the placebo arm, to at least 22% in the vaccine arm.

For the secondary objectives of immunogenicity, approximately 300 pregnant women will be enrolled in this study, 150 participants at the selected GBS6 dose/formulation (75 HIV positive and 75 HIV negative) and 150 participants in the placebo group (75 HIV positive and 75 HIV negative). Based on data from a recent study (20), the standard deviation (SD) of the GMT responses to serotypes Ia, Ib and III is expected to be around 2.55 log e units.

With 75 women per group, the study will have at least 80% power (5% alpha) to detect at least 3.24-fold higher antibody responses post-vaccination in vaccinated participants compared with placebo.

	HIV-uninfected pregnant women	HIV-infected pregnant women
Placebo	Group 1 (n=75)	Group 3 (n=75)
GBS6 vaccine	Group 2 (n=75)	Group 4 (n=75)

6.2 Study populations

Safety population

A safety population will be defined separately for, maternal participants and their infant participants. For the safety analyses, maternal participants will be analysed according to the investigational product received and infant participants will be analysed according to the investigational product their mothers (maternal participants) received.

- Maternal participants: All maternal participants receiving a dose of GBS6 or placebo will be included in the safety population.
- Infant participants: All infant participants who are enrolled in the study will be included in the safety population.

Immunogenicity population

Two populations will be defined separately for maternal participants and their infant participants: evaluable immunogenicity population and modified intent-to-treat (mITT) populations. Immunogenicity data will be analysed separately for maternal participants and their infant participants.

For the immunogenicity analyses, maternal participants will be analysed according to the investigational product received for the evaluable immunogenicity population and the investigational product as randomised for the mITT population. Infant participants will be analysed according to the investigational product received by their mothers (maternal participants) for the evaluable immunogenicity population and the investigational product assigned to

their mothers (maternal participants) for the mITT population. The evaluable immunogenicity population is considered to be the primary population for the immunogenicity analyses.

- Maternal participants

To be included in the evaluable immunogenicity population, the maternal participant must have been eligible for the study, have received GBS6 or placebo as randomised, have had blood drawn within the specified time frames, have at least one valid and determinate assay result for the proposed analysis, and have no other major protocol violations. To be included in the mITT population, the maternal participant must be randomised and have at least one valid and determinate assay result related to the proposed analysis.

- Infant participants

To be included in the evaluable immunogenicity population, the infant participant must have been eligible for the study, the infant participant's mother must have received GBS6 or placebo as randomised, and the infant participant must have had blood drawn within the specified time frames, have at least one valid and determinate assay result for the proposed analysis, and have no other major protocol violations. To be included in the mITT population, the infant participant's mother must be randomised and the infant participant must have at least one valid and determinate assay result related to the proposed analysis.

6.3 Statistical methods

Safety data will be analysed separately for maternal participants and their infant participants.

- Descriptive analysis

A flowchart will be used to summarise the number of mothers approached, consented, recruited, assigned to the different study arms, receiving the intended vaccines, completing the study protocol and analysed for the primary outcome, as recommended by the CONSORT statement (http://www.consort-statement.org/).

- Statistical significance and confidence intervals

5% significance will be used and 95% confidence intervals.

- Statistical software

Statistical analyses will be performed on STATA version 15 or similar.

- Missing data

Analysis will be by modified intention to treat (mITT), meaning individuals are analysed according to the group they are randomised to, but only those with at least one blood taken and antibody result will be included, with missing data (e.g. from withdrawals, non-compliers) assumed missing at random. Missing data will be excluded from relevant analyses. The mITT analysis will include blood samples taken outside the recommended timing. A per-protocol analysis will also be performed if there are major protocol deviations. Spurious data will be checked to source records and investigated but included if no cause is identified.

- Outliers, censored data and non-normal data

Outliers will be included in the analyses and investigated assuming no errors have occurred. We will assign all results of <2 a value of 1 for calculation of geometric means. Antibody concentrations will be log-transformed for analyses of mean antibody levels.

- **Statistical analysis for each objective and outcome**

Statistical Analysis of primary endpoints

The followings are the primary analyses for each of the outcomes related to primary objectives.

- Maternal primary endpoint 1:

Proportion of maternal participants reporting solicited local reactions within 7 days following administration of GBS6 vaccine will be calculated with exact binomial 95% confidence

intervals for each group. Comparison between groups (GBS v Placebo within each HIV strata) will be by Fisher's exact test.

- Maternal primary endpoint 2:

Proportion of maternal participants reporting solicited systemic events within 7 days following administration of GBS6 vaccine will be calculated with exact binomial 95% confidence intervals for each group. Comparison between groups (GBS v Placebo within each HIV strata) will be by Fisher's exact test.

- Maternal primary endpoint 3:

Proportions of maternal participants reporting solicited and unsolicited adverse events through 1 month following administration of GBS6 vaccine will be calculated with exact binomial 95% confidence intervals for each group. Comparison between groups (GBS v Placebo within each HIV strata) will be by Fisher's exact test.

- Maternal primary endpoint 4:

Proportions of maternal participants with SAEs, MAEs, and obstetric complications (peripartum, intrapartum, and postpartum) throughout the study (Visit 1 through the 12-month postdelivery study visit) and any unsolicited events leading to study withdrawal following administration of GBS6 vaccine will be calculated with exact binomial 95% confidence intervals for each group. Comparison between groups (GBS v Placebo within each HIV strata) will be by Fisher's exact test.

- Infant primary endpoint 1:

Proportions of infants with unsolicited adverse events from birth to 6 weeks of age month following administration of GBS6 vaccine will be calculated with exact binomial 95% confidence intervals for each group. Comparison between groups (GBS v Placebo within each HIV strata) will be by Fisher's exact test.

◦ Infant primary endpoint 2:

Proportions of infants with SAEs, AEs of special interest (major congenital anomalies, developmental delay, and suspected or confirmed GBS infection), and MAEs through 12 months of age and any unsolicited events leading to study withdrawal following administration of GBS6 vaccine will be calculated with exact binomial 95% confidence intervals for each group. Comparison between groups (GBS v Placebo within each HIV strata) will be by Fisher's exact test.

Statistical analysis of secondary endpoints

The followings are the primary analyses for each of the outcomes related to secondary objectives.

• Maternal secondary endpoint 1:

Antibody levels for GBS serotype-specific antibody concentrations measured at baseline, 2 weeks, 1 month after vaccination, at delivery, and 6 weeks after delivery in HIV positive and HIV negative women will be described using box-and-whisker plots with a log-scale y-axis. GMTs of GBS serotype specific antibody concentrations measured at baseline, 2 weeks, 1 month after vaccination, at delivery, and 6 weeks after delivery in HIV positive and HIV negative women will be calculated with 95% confidence intervals post vaccinations and the groups will be compared using unpaired t-tests or the Kruskal Wallis test if log-titres are not normally distributed.

Reverse cumulative distribution curves (RCDCs) of antibody concentrations by vaccine groups will be generated for each GBS6 serotype. Additionally, graphs of geometric means and the associated 95% CIs of the antibody concentrations will be presented at each analysis time point by vaccine group and serotype. The proportions of participants achieving defined GBS6 serotype specific IgG concentrations will be summarised descriptively at prespecified time points as counts and percentages with 2-sided 95% exact CIs by vaccine group and HIV

status. Groups 1 vs 2, 3 v 4 will be compared by a t-test or Kuskal-Wallis test if logged data are not normally distributed.

- Maternal secondary endpoint 2:

For each serotype, GBS serotype specific IgG GMT measured at baseline, and at delivery in HIV positive and HIV negative women will be calculated for each group with 95% confidence intervals. Groups 1 vs 2, 3 v 4 will be compared using similar methods to those for IgG concentrations.

- Infant secondary endpoint 1:

GMCs of GBS serotype specific IgG concentrations in HIV-exposed and unexposed infant participants measured at birth, 18 weeks and 12 months of life will be calculated at all blood draw visits for each group with 95% confidence intervals. Groups 1 vs 2, 3 v 4 will be compared using similar methods to those for maternal IgG concentrations.

- Infant secondary endpoint 2:

GMTs of GBS serotype specific IgG GMT in HIV-exposed and unexposed infant participants measured at 18 weeks of life will be calculated for each group with 95% confidence intervals. Groups 1 vs 2, 3 v 4 will be compared

- Infant secondary endpoint 3:

For each serotype, placental transfer ratio (infant GMC in cord blood or infant blood collected within 72 h of birth divided by maternal GMC in blood collected at delivery) will be calculated for each group with 95% confidence intervals. Groups 1 vs 2, 3 v 4 will be compared using similar methods to those for IgG concentrations.

Statistical analysis of exploratory endpoints

The followings are the primary analyses for each of the outcomes related to exploratory objectives.

• Maternal exploratory endpoint 1: The geometric mean fold ratio with a two-sided 95% CI will be calculated for group 4/group2. To account for differences between HIV positive and negative mothers the ratio of group 4/group 2 will be adjusted in a normal errors regression model on logged titers with terms included for covariates including maternal age, gestation and birth weight.

Maternal exploratory endpoint 2: Proportions of maternal participants with GBS colonisation assessed by vaginal and rectal swab before vaccination, at delivery, and 6 weeks after delivery will be calculated with exact binomial 95% confidence intervals for each group. Comparison between groups (GBS v Placebo within each HIV strata) will be by Fisher's exact test.

• Maternal exploratory endpoint 3: For each serotype, IgA/IgG GMCs will be calculated at all breast milk visits for each group with 95% confidence intervals. Groups 1 vs 2, 3 v 4 will be compared using similar methods to those for blood IgG concentrations.

• Infant exploratory endpoint 1: The proportion of infant participants achieving defined levels of IgG to diphtheria toxoid and 13-valent pneumococcal conjugate vaccine serotypes will be summarised descriptively at 18 weeks and 12 months of age. Groups 1 vs 2, 3 v 4 will be compared using similar methods to those for GBS IgG concentrations.

• Infant exploratory endpoint 2: Proportions of infant participants with GBS colonisation assessed by nasal/rectal swabs at birth and at 6 weeks and 18 weeks of age will be calculated with exact binomial 95% confidence intervals for each group. Comparison between groups (GBS v Placebo within each HIV strata) will be by Fisher's exact test.

• Infant exploratory endpoint 3: For each serotype, GMCs will be calculated from dried blood spots in infant participants at births for each group with 95% confidence intervals.

Note that detailed analyses of all the endpoints including additional exploratory analyses and graphical displays will be described in the SAP.

7. Trial design

This is a randomised, placebo controlled, double-blind, parallel group study which will be based at Kawempe Specialised National Referral Hospital, Kawaala and Komamboga Health Centre III and Wakiso and Kisenyi Health Centre IV, Uganda.

Subjects will be a randomized 1:1 to GBS6/placebo stratified by baseline HIV status:

1. HIV-uninfected women, placebo (saline) in pregnancy;
2. HIV-uninfected women, GBS6 in pregnancy;
3. HIV-infected women, placebo (saline) in pregnancy;
4. HIV-infected women, GBS6 in pregnancy;

	HIV-uninfected pregnant woman	HIV-infected pregnant woman
Placebo (saline) in pregnancy	Group 1 (n=75)	Group 3 (n=75)
GBS6 in pregnancy	Group 2 (n=75)	Group 4 (n=75)

8. Participant Selection criteria

There will be no exceptions (waivers) to eligibility criteria prior to participant inclusion into the study. Any questions raised about eligibility should be addressed prior to enrolling the participant.

The eligibility criteria have been carefully considered and are standards used to ensure the trial results can be appropriately used to make future treatment decisions for other people with similar disease or medical condition. It is therefore vital that exceptions are not made to the following detailed selection criteria.

8.1. Inclusion criteria for Maternal Participants

1. Age ≥ 18 to ≤ 40 years of age, inclusive at day of signing the ICF.
2. Pregnant at ≥ 27 0/7 to ≤35 6/7 gestation on the day of planned vaccination, verified by ultrasound scan (U/S).
3. Low risk, singleton pregnancy, as assessed by the study physician based on ultrasound scan and previous obstetric history.
4. Documented negative HBV surface antigen, HCV antibody, and syphilis tests at screening.
5. Normal full blood count (CBC), renal and liver function tests at screening.
6. Documented HIV test during pregnancy undertaken as per the national guidelines.
7. If HIV infected pregnant women, stable on ART for at least 2 months prior to study start with an undetectable viral load (VL)
8. Determined by medical history, physical examination, screening laboratory assessment, and clinical judgment to be appropriate for inclusion in the study.
9. Receiving prenatal standard of care including HIV care if applicable at the clinics/physician offices/hospital network affiliated with the clinical study site.
10. Willing to give birth at Kawempe Specialised National Referral Hospital, Kawaala or Komamboga Health Centre III or Wakiso or Kisenyi Health center IV, Uganda.

11. Willing and able to participate for the duration of the study visits and follow-up until 12-months post-delivery.
12. Willing and able to be contacted by telephone for the full duration of the study, and to give informed consent for their infant participant to participate in the study.

8.2. Inclusion criteria for Infants

Inclusion criteria for Infants

1. Parent(s) willing and able to comply with scheduled visits, investigational plan, laboratory tests, and other study procedures.

8.3. Exclusion criteria for Maternal Participants

Any of the following:

1. Investigator site staff members directly involved in the conduct of the study and their family members, site staff members otherwise supervised by the investigator, or participants who are Pfizer employees, including their family members, directly involved in the conduct of the study.
2. Participants whose unborn baby have been fathered by investigational site staff members directly involved in the conduct of the study or their family members, site staff members otherwise supervised by the investigator, or Pfizer employees directly involved in the conduct of the study.
3. Participation in other studies involving investigational drug(s), vaccines, or medical devices within 28 days prior to study entry and/or during study participation.
4. Previous vaccination with any licensed or investigational GBS vaccine.
5. History of severe adverse reaction associated with a vaccine and/or severe allergic reaction (e.g., anaphylaxis) to any component of the investigational product.
6. History of microbiologically proven invasive disease caused by GBS, or history of an infant with GBS disease.
7. Current alcohol abuse or illicit drug use.

8. Body mass index (BMI) of ≥40 kg/m^2 at the time of the screening visit.

9. Clinical history of primary genital herpes simplex virus (HSV) infection during the current pregnancy.

10. A prior history of or current pregnancy complications or abnormalities that will increase the risk associated with the participant's participation in, and completion of, the study, including but not limited to the following :

a. Gestational hypertension or preeclampsia-eclampsia
b. Placental abnormality
c. Polyhydramnios or oligohydramnios
d. Significant bleeding or blood clotting disorder
e. Gestational diabetes
f. Any signs of premature labour with the current pregnancy

11. Prior late stillbirth (defined as loss of pregnancy at any time after 28 weeks gestation) or neonatal death (defined as death of an infant within the first 28 days of life), prior low birth weight baby (defined as infant <2500 g) or premature delivery (defined as delivery before 37 0/7 weeks gestation), prior history of at least 3 miscarriages, prior pregnancies numbering greater than 5, or previous infant with a known or suspected genetic disorder or major congenital anomaly

12. Confirmed GBS bacteriuria during the current pregnancy

13. Major illness of the mother (outside of HIV serostatus) or conditions of the foetus that, in the investigator's judgment, will substantially increase the risk associated with the participant's participation in, and completion of, the study or could preclude the evaluation of the participant's response, including but not limited to the following:

a. hypertension requiring treatment
b. heart disease
c. lung disease
d. neurological disorders including a history of epilepsy or recurrent afebrile seizures

e. kidney disease

f. liver disease

g. haematological disorders (including sickle cell disease)

h. severe anaemia (less than 7.0g/dL)

i. significant bleeding or blood clotting disorder

j. endocrine disorders including known diabetes mellitus

14. Participants with known or suspected immunodeficiency (outside of HIV positive sero-status).

15. Participants who receive treatment with immunosuppressive therapy including cytotoxic agents or systemic corticosteroids, e.g., for cancer or an autoimmune disease, or planned receipt through the postvaccination blood draw. Inhaled/nebulised, intra-articular, intra-bursal, or topical (skin or eyes) corticosteroids are permitted.

16. Receipt of blood/plasma products or immunoglobulin, from 60 days before investigational product administration, or planned receipt through delivery.

17. Known to be Rhesus Negative

18. Psychiatric condition including recent (within the last year) or active suicidal ideation or behaviour or laboratory abnormalities that may increase the risk associated with study participation or investigational product administration or may interfere with the interpretation of study results and, in the judgment of the investigator, would make the participant inappropriate for entry into this study.

19. Deprived of freedom by an administrative or court order, or in an emergency setting, or hospitalised involuntarily.

8.4. Duration of participant participation

Each participant will participate In the study for up to approximately 16 months.

8.5. Temporary Delay Criteria

The following conditions are temporary or self-limiting and a participant may be vaccinated once the condition(s) has/have resolved and no other exclusion criteria are met.

Criteria for temporarily delaying vaccine administration

- Current febrile illness (body temperature ≥38^{0}C [≥100.4^{0}F]) or other acute illness within 48 hours before investigational product administration.

- Receipt of any inactivated vaccine in the 14 days and any live vaccine within the 28 days before investigational product administration.

- Receipt of short term (<14 days) systemic corticosteroids. Investigational product administration should be delayed until systemic corticosteroid use has been discontinued for at least 30 days. Inhaled/nebulised, intraarticular, intra-bursal, or topical (skin or eyes) corticosteroids are permitted.

8.6. Discontinuation/withdrawal of participants

A study participant will be discontinued from participation in the study if:

(i) Any medical condition or situation occurs such that continued participation in the study would not be in the best interest of the participant.

(ii) Laboratory-confirmed documented GBS infection in this pregnancy.

For further details on participant's premature termination see corresponding section below.
Participants are free to withdraw from the study at any time without giving a reason.
Any data collected up to the point of withdrawal will continue to be used in the study analyses unless specifically requested by the participant.

8.7. Study stopping rules

Safety will be evaluated according to the stopping rules defined below. Stopping rules will be in effect and apply as detailed below to subjects enrolled in the study and will apply only to GBS6 vaccinated subjects. Diary data confirmed to be entered by the subject in error will not contribute toward a stopping rule.

If it is suspected that a stopping rule has been met based on blinded safety assessment, the sponsor's designated unblinded personnel (and their backup designees) will seek to verify whether a stopping rule has been met based on unblinded randomization information. During this verification process, the investigational site will be instructed by the sponsor not to administer any further investigational product. If the unblinded sponsor personnel determine that a stopping rule has not been met, then the sponsor will notify investigational sites that administration of the investigational product may continue according to the clinical trial protocol.

In the event that the unblinded sponsor personnel confirm that a stopping rule is met, enrollment and administration of the investigational product will not continue until the DSMB has reviewed all safety data and provided recommendations to the study team. The School of Medicine Research and Ethics Committee (SOMREC), Uganda National Council for Science and Technology (UNCST), national drug authority (NDA) and the sponsor will be notified of study hold.

If, after the safety review by the DSMB, it is appropriate to restart the trial without a protocol amendment, SOMREC, UNCST & NDA will be notified and the study restarted, however if the DSMB recommends a protocol amendment the study principal Investigator will notify SOMREC, UNCST & NDA of the decision by the DSMB. The protocol amendment will be submitted to the SOMREC, Uganda National Council for Science and Technology (UNCST) and

national drug authority (NDA) for approval. The trial will not restart until the amendment has been approved by the NDA, UNCST and SOMREC.

Although enrollment and vaccination activities will stop until DSMB review is complete and the issue is resolved, all other routine study conduct activities such as ongoing data entry, reporting of AEs, subject e-diary completion, subject follow-up including blood draws, etc, must continue during this time.

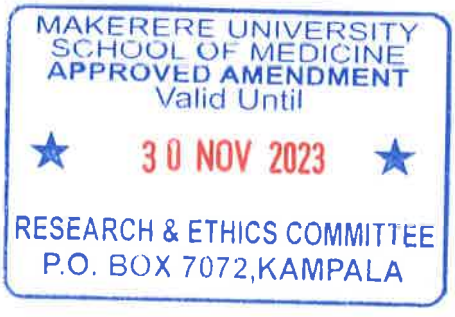
A stopping rule will be considered to have been met if any of the following occur:

a) If any GBS6 vaccinated subject develops an SAE within 30 days following vaccination for which there is no other clear attributable cause, or if the investigator determines that the SAE is related to vaccination.

b) If any GBS6 vaccinated subject experiences a prompted local reaction or systemic event considered related to vaccination that results in an emergency room visit, or a local equivalent to this type of visit, or has local necrosis or exfoliative dermatitis (Grade 4 event) within 7 days following vaccination, or a Grade 4 laboratory abnormality at or before the 2-week postvaccination visit.

c) If more than 6 GBS6 vaccinated subjects experience the same Grade 4 local reaction or systemic event within 7 days following vaccination, not attributable to any other cause, including:

i. Local redness
ii. Local swelling
iii. Local pain
iv. Headache
v. Fatigue
vi. Joint pain
vii. Muscle pain
viii. Nausea/vomiting



ix. Diarrhea

d) If more than 2 GBS6 vaccinated subjects experience the same or similar Grade 3 or 4 unsolicited AE within 7 days following vaccination, or laboratory abnormality at or before the 2-week postvaccination visit, not attributable to any other cause.

e) If more than 2 GBS6 vaccinated subjects experience fever greater than 39.0°C (greater than 102.1°F) for more than 2 consecutive days within 7 days following vaccination, for which there is no other clear attributable cause.

f) If any GBS6 vaccinated subject experiences a confirmed fever >40.0°C (>104.0°F) for 1 daily measurement within 7 days following vaccination, for which there is no other clear attributable cause.

g) If more than 2 GBS6 vaccinated subjects experience premature labor or premature rupture of membranes within 14 days after vaccination.

h) If any GBS6 vaccinated subject experiences severe vaginal bleeding (eg, partial abruption), severe preeclampsia, eclampsia, HELLP (hemolysis, elevated liver enzymes, and low platelet count) syndrome, or life threatening sequelae of preeclampsia (eg, pulmonary edema), stillbirth, or fetal loss within 14 days after vaccination.

i) If any GBS6 vaccinated subject develops an SAE during participation in the study following vaccination for which the investigator determines that the SAE is related to vaccination.

9. Methods

9.1. Study population

HIV-infected and uninfected pregnant women aged 18-40 years who will be attending Ante-natal care at Kawempe National Referral Hospital, Kawaala or Komamboga Health Centre III or Wakiso or Kisenyi Health Centre IV, Uganda and who meet the inclusion criteria.

Kawempe national referral hospital is a national referral hospital, while Kawaala and Komamboga Health Centre III and Wakiso and Kisenyi health centre IV are health centres under the Kampala Capital City Authority.

All hospitals have fully equipped emergency area including resuscitation and operation rooms. Both hospitals have fully equipped antenatal, labour and delivery, post-natal and EPI services.

9.2. Data collection

Data will be collected regarding: previous vaccinations (mother), parity, gravida, illnesses or complications of pregnancy, gestation at birth, birth weight, HIV status (mother and infant), syphilis and hepatitis B and hepatitis C status, CBC, renal and liver function, CD4 count, HIV viral load, medications, maternal age, ethnicity, infant sex and number of siblings. All patient information will be directly inputted into the database using only the unique study identifier.

9.3. Patient randomisation

Participants will be randomized to either receive one dose of GBS6 vaccine or Placebo as a single injection on Day 1.

Stratified Block randomization will be used in this study. Randomization will be done in blocks of eight (8) in an automated system of Stata, stratified by HIV status and the list uploaded in the REDCap database. Participants will be randomized onto either arm (trial vaccine or placebo) of the study at enrolment by the data manager. The groups within REDCap will be labelled (A and B) and only the data manager will have access to the randomization

CRF, but the data manager will not be aware of which group (A or B) is the trial vaccine or placebo. Equal numbers will be allocated into each group (total n=300, 75 per group), with randomisation stratified by HIV status.

During the screening visit, the Data Manager will enter the participant's Screening ID into the REdCap system and complete the Randomization eCRF to randomise a participant. Once the participant is randomised, the RedCAP system will randomly allocate the participant to either arm A or B as above. This will be notified automatically to the unblinded pharmacist. The unblinded pharmacist will take the notification and prepare the vaccine/placebo accordingly. The participants will use the same randomisation number throughout the study. The pharmacist will retain the lists of the allocation of unblinded medication prepared. The list must be kept in a safe place away from the blinded study team and will be monitored by the unblinded monitor.

9.4. Blinding of the Site Personnel

This is a double blinded study. Study nursing staff and participants will be blinded to the vaccine given and vaccine syringes will be covered with an opaque label, obscuring the vaccine. Only the preparing pharmacist(s) (unblinded dispenser(s)) will be aware of the vaccine used. The vaccine will be administered by a trained nurse who will only give the vaccine and have no other participation in the study. A study nurse who is blinded to the vaccine given will observe for immediate reactions to the vaccine in a separate room from where the woman will receive her vaccination. This room will have an emergency trolley with appropriate drugs available should these be required. At least one unblinded dispenser and a backup will be assigned. A member of the study site staff not responsible for monitoring safety in the study or clinic pharmacy should fulfill this role. Contact between the unblinded dispenser(s) and study participants should be kept to a minimum. The investigator, study coordinator, and any site staff other than the unblinded dispenser(s)

must not be allowed to know the investigational product assigned to any study participant and must not be allowed to see the investigational product containers. The laboratory-based research team conducting the assays will be blinded to subject allocation.

9.5. Blinding of the Sponsor

In this study, the sponsor study team members will remain blinded to vaccine assignment of all participants enrolled. Laboratory personnel performing the serological assays will remain blinded to vaccine assigned/received throughout the study.

9.6. Schedule of activities (refer to Table 1 and 2)

Maternal participant

Screening: 2x5mls blood drawn for HBV, HCV, HIV and syphilis, CBC, renal and liver function testing. ICF, review medical history, dating ultrasound and review eligibility criteria. Review pregnancy immunisation history to endure participants have had two doses of tetanus vaccines at least 14 days prior to GBS6 immunisation. To test for glucose and protein, urine samples will be obtained.

Visit 1 (Day 1): Maternal participant will be administered GBS6 or placebo. 1x10mls blood drawn for immunogenicity assessment. To determine GBS status, one rectal and one vaginal swab will be performed. 1x5mls blood drawn for CD4 and viral load testing. Women will be asked to keep a symptom diary for 7 days post vaccination.

Visit 2 (2-weeks follow-up visit): 1x10mls blood drawn for immunogenicity assessment.

Visit 3: (1-month follow-up visit): 1x10mls blood drawn for immunogenicity assessment.

Visit 4 (Delivery): 1x10mls blood drawn for immunogenicity assessment and one rectal and one vaginal swab to determine GBS status. 1x2mL of colostrum (within 72 hours of birth)

Visit 5 (1 week post delivery): telephone call to check on health

Visit 6 (6-weeks post-delivery): 1x10mls blood drawn for immunogenicity assessment and one rectal and one vaginal swab to determine GBS status. 1x5mL of breastmilk

Visit 7 (18 weeks post delivery): 1x5mL breastmilk, urine pregnancy test (dipstick)

Visit 8 (6 months post-delivery): telephone call to check on health and pregnancy.

Visit 9 (12-months post-delivery): 1x10mls blood drawn for immunogenicity assessment, urine pregnancy test (dipstick).

If any participant is found to be pregnant in any visit from Visit 7-9 then they will be asked for permission to follow this subsequent pregnancy and directed to antenatal care. No additional investigations or visits are planned in the event that a participant has a subsequent pregnancy but data collection will occur in addition to the original pregnancy to assess safety (see section 14.14.2. below).

Infant participant

Visit 4 (Delivery): 1x10mls cord blood drawn for immunogenicity assessment, dried blood spot card collection and nasal/rectal swab to determine GBS status.

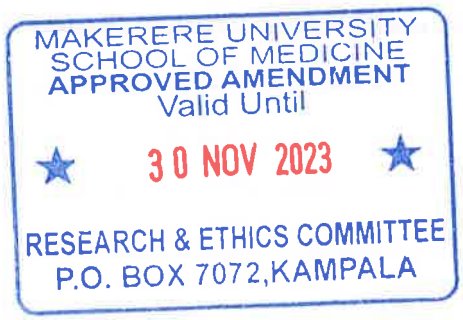
Visit 5 (1 week post-delivery): telephone call to check on health

Visit 6 (6-weeks post-delivery): Infant ~5mls blood at 6 weeks and nasal/rectal swab to determine GBS status.

Visit 7 (18-weeks post-delivery): Infant ~5mls blood and nasal/rectal swab to determine GBS status.

Visit 8 (6 months post-delivery): telephone call to check on health

Visit 9 (12-months post-delivery): Infant ~5mls blood at 12 months.



10. Trial Investigational Product

All maternal participants will receive either a placebo or GBS6. This vaccine will be given at the time period assigned by randomisation. **No vaccine will be given as part of the study at ≤ 26 6/7 Gestational weeks as per inclusion/exclusion criteria.**

10.1. Investigational Product Supplies

GBS6 and placebo (saline control) will be provided by Pfizer.

Study vaccines will be packed and labeled as investigational product in accordance with current guidelines and applicable local and legal regulatory requirements. The formulation of the investigational products is described below.

10.2. Name and description of investigational medicinal product (IP)

The investigational products are GBS6 and placebo (saline control). The GBS6 will be 20mcg without AlPO4 (equivalent to 240 mcg/mL) /0.5mL dose or 20 mcg CPS/serotype)

Participants will receive 1 dose of GBS6,without $AlPO_4$, or placebo (saline control) at Visit 1 administered intramuscularly by injecting 0.5 mL into the deltoid muscle, preferably of the nondominant arm.

10.3. Preparation and Dispensing

Investigational product preparation and dosing information will be provided in the investigational product (IP) manual.

GBS6 and placebo will be prepared by qualified unblinded site personnel according to the IP manual. The investigational product will be administered by qualified unblinded site personnel who keep the participants blinded, because of the difference in investigational product appearance.

Please refer to the IP manual for instructions on how to prepare the investigational product for administration.

10.4. Allocation to Investigational Product

The unblinded pharmacist will take the notification generated by the REDCap system described above and prepare the vaccine/placebo accordingly. The participants will use the same randomisation number throughout the study. The pharmacist will retain the lists of the allocation of unblinded medication prepared. The list must be kept in a safe place away from the blinded study team and will be monitored by the unblinded monitor. The pharmacist will indicate the randomisation number on the blinded vaccine for the study team to inject. The filled syringes will be covered with opaque tape to ensure that the participant is blinded to the allocation.

The participants will be allocated to an investigational product group as described above. Infants (infant participants) of the maternal participants will be assigned a participant number at birth.

10.5. Participant compliance

All doses of investigational product will be administered by the appropriately designated study staff at the investigator site.

10.6. Administration

Standard vaccination practices must be observed and vaccine must not be injected into blood vessels. Appropriate medication and other supportive measures for management of an acute hypersensitivity reaction should be available in accordance with local guidelines for standard immunisation practices.

Preparation and administration of investigational products should be performed by an appropriately qualified, Good Clinical Practice (GCP)trained, and vaccine experienced member of the study staff (e.g., physician, nurse, physician's assistant, nurse practitioner, pharmacist, or medical assistant) as allowed by local, state, and institutional guidance.

Investigational product administration details will be recorded on the case report form (CRF).

The participants will receive 1 dose/formulation of either GBS6 or placebo (saline control) at Visit 1 in accordance with the study's schedule of activities.

GBS6 or placebo (saline control) should be administered intramuscularly by injecting 0.5 mL into the deltoid muscle, preferably of the nondominant arm.

10.7. Investigational Product Storage (including blinded GBS6 and placebo)

The investigator or an approved representative, e.g., pharmacist, will ensure that all investigational products are stored in a secured area with controlled access under required storage conditions and in accordance with applicable regulatory requirements. Investigational products should be stored in their original containers and in accordance with the labels until they are prepared for administration by the unblinded pharmacist.

Investigational product will be shipped at +2^{0}C to +8^{0}C to each study site after required regulatory and legal documents have been received by the sponsor. Upon receipt at the study site, the investigational product should be immediately transferred to a +2^{0}C to +8^{0}C temperature-monitored refrigerator for storage.

The unblinded dispenser/administrator will ensure that all investigational products are stored in a secured area with controlled access under required storage conditions and in accordance with applicable regulatory requirements.

Site systems must be capable of measuring and documenting (for example, via a log), at a minimum, daily minimum and maximum temperatures for all site storage locations (as applicable, including frozen, refrigerated, and/or room-temperature products). This should be captured from the time of investigational product receipt throughout the study. Even for continuous-monitoring systems, a log or site procedure that ensures active evaluation for excursions should be available. The intent is to ensure that the minimum and maximum temperature is checked each business day to confirm that no excursion occurred since the last evaluation and to provide the site with the capability to store or view the minimum/maximum temperature for all nonworking days upon return to normal operations. The operation of the temperature monitoring device and storage unit (for example, refrigerator), as applicable, should be regularly inspected to ensure they are maintained in working order.

Any excursions from the product label storage conditions should be reported to Pfizer upon discovery. The site should actively pursue options for returning the product to the storage conditions described in the labeling, as soon as possible. Deviations from the storage requirements, including any actions taken, must be documented and reported to Pfizer. Receipt of materials, door opening and closing, and other routine handling operations where the products are briefly out of the temperature range described in the must be documented and reported to Pfizer .

Once an excursion is identified, the investigational product must be quarantined and not used until Pfizer provides permission to use the investigational product. It will not be considered a protocol deviation if Pfizer approves the use of the investigational product after the temperature excursion. Use of the investigational product prior to Pfizer approval will be considered a protocol deviation. Specific details regarding information the site should report for each excursion will be provided to the site in the IP manual.

10.8. Accountability procedures for the IP(s)

The unblinded dispenser/administrator at the investigator site must maintain adequate records documenting the receipt, use, loss, or other disposition of the investigational product supplies. All investigational products will be accounted for using a drug accountability form/record.

10.9. Concomitant treatment

Prohibited non-study vaccines and medications during study

- Investigational vaccines, drugs, or medical devices are prohibited during the course of the study.
- Blood/plasma products or immunoglobulins (except antiD immunoglobulin, e.g., RhoGAM, which can be given at any time), and immunosuppressive therapy are prohibited during the course of the study. Unless clinically indicated by the hospital team.
- Other non-study vaccines (including diphtheria- and CRM_{197}-containing vaccines) may not be given concomitantly with the investigational product or within 14 days before or after investigational product administration (except during an outbreak or pandemic situation).

Permitted non-study vaccine and medications during the study

10.9.1. Maternal participants

- Tetanus containing vaccines (TT and Td) may be given during the study from 14 days before or after investigational product administration as per local recommendations for immunisation in pregnant women. Influenza vaccines may be given during the study from 14

days before or after investigational product administration as per local recommendations for immunisation in pregnant women.

- Inhaled/nebulised, intra-articular, intra-bursal, or topical (skin or eyes) corticosteroids are permitted.

- The use of antipyretics and other pain medication to treat symptoms associated with investigational product administration is permitted during participation in the study.

- The use of prophylactic antipyretic medication, while permitted, is not recommended on the day prior to vaccination or the day of the investigational product administration.

- As long as not part the exclusion criteria, concomitant medications are permitted, and they will be recorded.

The standard of care for prevention of GBS disease in infants will be applicable to all pregnant women enrolled in the study in accordance with local recommendations/guidelines.

10.9.2. Infant participants

Any routine vaccination given as part of the national recommended vaccination schedule for infants will be administered.

10.10. Prescribing & Dispensing of IP

The Research pharmacy will construct a protocol specific Clinical Trial Procedure which will detail participant management in relation to IP dosing and pharmacy dispensing procedures. The research pharmacy will also provide a study specific prescription template which may be used for the study.

All IP prescriptions presented to MUJHU pharmacy must be signed and dated by an approved prescriber. The prescriber must have been signed off by the PI on the Staff delegation of duties log for that task. A sample signature of all delegated prescribers must be provided for the Pharmacy Site File prior to receipt of the 1st trial prescription.
All vaccine will be supplied through Pfizer Inc and their handling and management will be participant to MUJHU and EPI standard policies.

10.11. Discontinuation/withdrawal of participants

In consenting to the trial, participants are consenting to trial treatments, trial follow up and data collection. However, an individual participant may stop treatment early or be stopped early for any one of the following reasons:

- Any change in participant's condition that in the investigator's opinion justifies the discontinuation of follow up
- Withdrawal of consent by the participant

As participation in the trial is entirely voluntary, the participant may choose to discontinue treatment at any time without penalties or loss of benefits to which they may be entitled. Although not obliged to give a reason for discontinuing their trial treatment/ protocol inclusion a reasonable effort should be made to establish this reason, whilst remaining fully respectful of the participant's rights. Participants who discontinue protocol treatment, for any of the above reasons, should remain in the trial for the purpose of safety follow up and data analysis.

If a participant withdraws consent, data that has already been collected should be kept and if the participant agrees analysed according to the ITT principle for all participants who stop follow up early. Participants who stop the trial follow up after receiving vaccination will not be replaced. Participants who withdraw prior to vaccination may be replaced.

11. Study procedure

11.1. Maternal participants

11.1.1 Visit 0- Screening

Participants will be screened from 2 to 14 days prior to administration of the investigational product to confirm that they meet eligibility (all of the inclusion and none of the exclusion) criteria for the study.

If the participant is found ineligible for the study on the basis of screening laboratory assessment and repeat testing is not warranted, the investigator may advise the participant of the results by telephone, and the participant will be withdrawn from further participation in the study. All eligible participants will proceed to Visit 1.

The following procedures will be performed:

- Obtain written informed consent before performing any study-specific procedures.
- Assign a single participant identifier using the RedCAP system.
- Obtain and record the participant demographic data (including date of birth, sex, race, and ethnicity). The complete date of birth (dd-mmm-yyyy) will be collected to critically evaluate the immune response and safety profile by age.
- Obtain and record current alcohol and tobacco usage.
- Obtain and record any medical and obstetric history of clinical significance including history from prior and current pregnancy(ies).
- Obtain and record any immunisation history during pregnancy such as tetanus containing vaccines (TT and Td) or influenza vaccines vaccination from prior and current pregnancy(ies).
- Record the last normal menstrual period (LMP) and estimated date of delivery (EDD).
- Measure vital signs, including weight, height, oral temperature, sitting blood pressure and pulse rate, and respiratory rate.

- Perform physical examination evaluating any clinically significant abnormalities within the following body systems: general appearance; skin; head, eyes, ears, nose, and throat; heart; lungs; abdomen; musculoskeletal; extremities; neurological; and lymph nodes. Abnormal results must be recorded on source documents and the physical examination page of the CRF.
- Perform obstetric examination including but not limited to scars from previous deliveries, fundal height, foetal heart tones, and foetal movement.
- Perform obstetric ultrasound and record findings.
- Ensure and document that all of the inclusion criteria and none of the exclusion criteria are met (see Section 8).
- Obtain blood sample (approximately 2 x 5 mL) for HBV, HCV, HIV, syphilis testing , CBC, renal and liver function. Participants newly testing positive for HIV, acute or chronic HBV, HCV, or syphilis will not be eligible for randomisation.
- Obtain urine sample for glucose and protein testing (urine dipstick).
- Complete the source documents.
- Record non-study vaccinations and medications (including antibiotic medications) as described in Section 10.9.
- The investigator or an authorised designee completes the CRF.

11.1.2 Visit 1- Vaccination (Day 1) Visit

- Review laboratory results.
- Ensure that the participant continues to be eligible for the study, meets none of the participants withdrawal criteria as described in Section 11.4, and meets none of the temporary delay criteria as described in Section 8.6.1.
- Prior to vaccination, measure vital signs, including weight, oral temperature, sitting blood pressure and pulse rate, and respiratory rate.

- Perform a targeted physical examination, evaluating any clinically significant abnormalities based on history and the participant's self-reported symptoms or complaints since the last visit.
- Perform obstetric examination including but not limited to fundal height, foetal heart tones, and foetal movement.
- Obtain urine sample for glucose and protein testing (urine dipstick).
- Issue the participant a paper diary card and provide instructions on its completion. Ensure that the participant records a baseline assessment of prompted systemic events in the paper diary card prior to vaccination.
- Prior to vaccination, collect a blood sample of approximately 10 mL for immunogenicity assessments and approximately 5 mL for CD4 count and viral load for HIV positive participants.
- Prior to vaccination, obtain one rectal and one vaginal swab for GBS microbiological culture.
- The unblinded dispenser dispenses the investigational product.
- The blinded administrator administers a single 0.5-mL injection of investigational product into the deltoid muscle, preferably of the nondominant arm.
- Blinded site staff must observe the participant for at least 30-minutes after investigational product administration for any acute reactions. Record any acute reactions in the participant's source documents and on the AE page of the CRF, and on an SAE form as applicable.
- Issue a measuring device to measure local reactions and a digital thermometer for recording daily temperatures, and provide instructions on their use.
- Ask the participant to complete the paper diary card from Day 1 to Day 7 (Day 1 is the day of vaccination).
- Ask the participant to contact the site staff or investigator immediately if prompted by the paper diary card from Day 1 to Day 7 following vaccination to determine if an

unscheduled visit is required (e.g., redness or swelling at the injection site measuring greater than 21 measuring device units [greater than 10.5 cm]).

- Remind participants that study staff may contact them to obtain additional information on Grade 3 events entered into the paper diary card.
- Ask the participant to contact the site staff or investigator if a medically attended event (e.g., emergency room) or hospitalisation occurs.
- Complete the participant's source documents.
- Record non-study vaccinations and all concomitant medications (including herbal remedies and antibiotic medications).
- The investigator or an authorised designee completes the CRF and an unblinded site staff member updates the investigational product accountability records.
- Designated site staff will review paper diary card data online at frequent intervals for the 7 days following vaccination to evaluate participant compliance and as part of the ongoing safety review.
- Geolocate the participant by accompanying them to their home if consented for this

11.1.3 Visit 2- Week-2 Follow-up visit

If delivery occurs before this visit, please conduct the delivery visit instead. For procedures to be conducted at delivery, see Section 11.1.5.

- Ensure that the participant continues to be eligible for the study and meets none of the participant withdrawal criteria as described in Section 11.4.
- Measure vital signs, including weight, oral temperature, sitting blood pressure and pulse rate, and respiratory rate.
- Perform a targeted physical examination, evaluating any clinically significant abnormalities based on history and the participant's self-reported symptoms or complaints since the last visit.

- Perform obstetric examination including but not limited to fundal height, foetal heart tones, and foetal movement.
- Collect a blood sample of approximately 10 mL for immunogenicity assessments.
- Review the participant's paper diary card data and collect the paper diary card. Collect stop dates of any paper diary card events ongoing on the last day that the paper diary card was completed and record stop dates in the CRF.
- Complete the participant's source documents.
- Record non-study vaccinations and all concomitant medications (including herbal remedies and antibiotic medications).
- Record AEs as described in Section 13 and 14.
- The investigator or an authorised designee completes the CRF.

11.1.4 Visit 3- 1 Month Follow-up visit

If delivery occurs before this visit, please conduct the delivery visit instead. For procedures to be conducted at delivery, see Section 11.1.5.

- Ensure that the participant continues to be eligible for the study and meets none of the participant withdrawal criteria as described in Section 11.4.
- Measure vital signs, including weight, oral temperature, sitting blood pressure and pulse rate, and respiratory rate.
- Perform a targeted physical examination, evaluating any clinically significant abnormalities based on history and the participant's self-reported symptoms or complaints since the last visit.
- Perform obstetric examination including but not limited to fundal height, foetal heart tones, and foetal movement.
- Collect a blood sample of approximately 10 mL for immunogenicity assessments.
- Complete the participant's source documents.

- Record non-study vaccinations and all concomitant medications (including herbal remedies and antibiotics).
- Record AEs as described in Section 13 and 14.
- The investigator or an authorised designee completes the CRF.

11.1.5 Visit 4- Delivery

- Ensure that the participant continues to be eligible for the study and meets none of the participant withdrawal criteria as described in Section 11.4.
- Record non-study vaccinations, any medication taken to treat AEs, and all concomitant medications (including herbal remedies and antibiotic medications).
- Collect a blood sample from the woman of approximately 10 mL for immunogenicity assessments. The blood sample may be collected up to 72 hours after delivery.
- Obtain one rectal and one vaginal swab for GBS microbiological culture. When the swabs cannot be taken at delivery, they may be taken after labour has started and up to 72 hours after delivery. .
- Collect 1-2ml sample of colostrum. The sample may be collected up to 72 hours after delivery. Participants will be asked to hand express a 1-2ml sample of colostrum. Participants will be provided with containers and instructions for the collection of samples.
- Complete the participant's source documents.
- Record AEs as described in Section 3 and 14.
- Record pregnancy outcome information.
- The investigator or an authorised designee completes the CRF.

11.1.6 Visit 5- 1-Week Postdelivery Follow-up (Telephone)

- Ensure that the participant continues to be eligible for the study and meets none of the participant withdrawal criteria as described in Section 11.4. This telephone

contact should be performed by the investigator or a medically qualified member of the study site staff.

- Complete the participant's source documents.
- Record any medication taken to treat AEs and all concomitant medications (including herbal remedies and antibiotic medications).
- Record AEs as described in Section 13 and 14.
- The investigator or an authorised designee completes the CRF.

11.1.7 Visit 6- 6-Week Post-delivery follow-up

- Ensure that the participant continues to be eligible for the study and meets none of the participant withdrawal criteria as described in Section 11.4.
- Perform a targeted physical examination, evaluating any clinically significant abnormalities based on history and the participant's self-reported symptoms or complaints since the last visit.
- Collect a maternal blood sample of approximately 10 mL for immunogenicity assessments.
- Collect breastmilk. Participants will be asked to hand express a 2-5ml sample of breastmilk. Participants will be provided with containers and instructions for the collection of samples.
- Obtain one rectal and one vaginal swab for GBS microbiological culture. .
- Complete the participant's source documents.
- Record any medication taken to treat AEs and all concomitant medications (including herbal remedies and antibiotic medications).
- Record AEs as described in Section 13 and 14.
- The investigator or an authorised designee completes the CRF.

11.1.8 Visit 7- 18 Week Post-delivery follow-up

- Ensure that the participant continues to be eligible for the study and meets none of the participant withdrawal criteria as described in Section 11.4.
- Complete the participant's source documents.
- Record any medication taken to treat AEs and all concomitant medications (including herbal remedies and antibiotic medications).
- Collect breastmilk. Participants will be asked to hand express a 2-5ml sample of breastmilk. Participants will be provided with containers and instructions for the collection of samples.
- Urine pregnancy test
- Record AEs as described in Section 13 and 14.
- The investigator or an authorised designee completes the CRF.

11.1.9 Visit 8- 6-Month Post-delivery follow-up (Telephone)

- Ensure that the participant continues to be eligible for the study and meets none of the participant withdrawal criteria as described in Section 11.4.
- Complete the participant's source documents.
- Record any medication taken to treat AEs and all concomitant medications (including herbal remedies and antibiotic medications).
- Check for possible pregnancy
- Record AEs as described in Section 13 and 14.
- The investigator or an authorised designee completes the CRF.

11.1.10 Visit 9- 12-Month Post-delivery follow-up

- Ensure that the participant continues to be eligible for the study and meets none of the participant withdrawal criteria as described in Section 11.4.
- Collect a blood sample of approximately 10 mL for immunogenicity assessments.

- Urine pregnancy test
- Complete the participant's source documents.
- Record any medication taken to treat AEs and all concomitant medications (including herbal remedies and antibiotic medications).
- Record AEs as described in Section 13 and 14.
- The investigator or an authorised designee completes the CRF.

11.2. Infant participants

11.2.1 Visit 1- Delivery

- Ensure that the participant continues to be eligible for the study and meets none of the participant withdrawal criteria as described in Section 11.4.
- Assign a single participant identifier.
- Record demography (including date of birth, sex, race, and ethnicity) and available birth information, including but not limited to infant participant vital status (live, stillbirth, neonatal death), appearance, pulse, grimace, activity, and respiration (Apgar) score, birth length, birth weight, head circumference, and Ballard score. The complete date of birth (dd-mmm-yyyy) will be collected to critically evaluate the antibody levels and safety profile by age.
- Record available vital signs, including axillary temperature, pulse rate, and respiratory rate.
- Record physical examination evaluating any clinically significant abnormalities within the following available body systems: general appearance; skin; head, eyes, ears, nose, and throat; heart; lungs; abdomen; musculoskeletal; extremities; genitourinary; back; neurological; and lymph nodes.
- Collect a cord blood sample of approximately 10 mL for immunogenicity assessments. If cord blood is unavailable, a blood sample of approximately 2.5 mL may be collected in the infant participants up to 72 hours after delivery.

- Blood spot card collection will be performed using the cord blood sample, or blood draw (up to 72 hours after delivery) if cord blood is unavailable. An additional blood spot card collection will be performed using an infant heel prick up to 72 hours after delivery. A single blood spot card will be collected using blood draw (up to 72 hours after delivery) if cord blood unavailable.
- Obtain nasal and rectal swab samples for GBS microbiological culture.
- Collect and record breastfeeding information.
- Complete the participant's source documents.
- Record AEs as described in Section 13 and 14.
- Record non-study vaccines and all concomitant medications (including herbal remedies and antibiotic medications).
- The investigator or an authorised designee completes the CRF.

11.2.2 Visit 2- 1-Week Postdelivery Follow-up (Telephone)

- Ensure that the participant continues to be eligible for the study and meets none of the participant withdrawal criteria as described in Section 11.4.
- Collect and record breastfeeding information.
- Complete the participant's source documents.
- Record AEs as described in Section 13 and 14.
- Record non-study vaccines and all concomitant medications (including herbal remedies and antibiotic medications).
- The investigator or an authorised designee completes the CRF.

11.2.3 Visit 3- 6-Week Post-delivery follow-up

- Ensure that the participant continues to be eligible for the study and meets none of the participant withdrawal criteria as described in Section 11.4.
- Measure vital signs, including weight, height, head circumference, axillary temperature, pulse rate, and respiratory rate.

- Perform physical examination evaluating any clinically significant abnormalities within the following body systems: general appearance; skin; head, eyes, ears, nose, and throat; heart; lungs; abdomen; musculoskeletal; extremities; genitourinary; back; neurological; and lymph nodes.
- Collect a blood sample of approximately 5 mL for immunogenicity assessments.
- Obtain nasal and rectal swab samples for GBS microbiological culture.
- Collect and record breastfeeding information.
- Complete the participant's source documents.
- Record AEs as described in Section 13 and 14.
- Record non-study vaccines and all concomitant medications (including herbal remedies and antibiotic medications).
- The investigator or an authorised designee completes the CRF.

11.2.4 Visit 4- 18-Week Post-delivery follow-up

- Ensure that the participant continues to be eligible for the study and meets none of the participant withdrawal criteria as described in Section 11.4.
- Measure vital signs, including weight, height, head circumference, axillary temperature, pulse rate, and respiratory rate.
- Perform physical examination evaluating any clinically significant abnormalities within the following body systems: general appearance; skin; head, eyes, ears, nose, and throat; heart; lungs; abdomen; musculoskeletal; extremities; genitourinary; back; neurological; and lymph nodes.
- Collect a blood sample of approximately 5 mL for immunogenicity assessments.
- Obtain nasal and rectal swab samples for GBS microbiological culture. .
- Collect and record breastfeeding information.
- Complete the participant's source documents.
- Record AEs as described in Section 13 and 14.

- Record non-study vaccines, any medication to taken treat AEs, and all concomitant medications (including herbal remedies and antibiotic medications).
- The investigator or an authorised designee completes the CRF.

11.2.5 Visit 5- 6-Months Post-delivery follow-up (Telephone)

- Ensure that the participant continues to be eligible for the study and meets none of the participant withdrawal criteria as described in Section 11.4.
- Collect and record breastfeeding information.
- Complete the participant's source documents.
- Record AEs as described in Section 13 and 14.
- Record non-study vaccines, any medication taken to treat AEs, and all concomitant medications (including herbal remedies and antibiotic medications).
- The investigator or an authorised designee completes the CRF.

11.2.5 Visit 6- 12-Months Post-delivery follow-up

- Ensure that the participant continues to be eligible for the study and meets none of the participant withdrawal criteria as described in Section 11.4.
- Measure vital signs, including weight, height, head circumference, axillary temperature, pulse rate, and respiratory rate.
- Perform physical examination evaluating any clinically significant abnormalities within the following body systems: general appearance; skin; head, eyes, ears, nose, and throat; heart; lungs; abdomen; musculoskeletal; extremities; genitourinary; back; neurological; and lymph nodes.
- Perform developmental assessment using *Ages and Stages* questionnaires.
- Collect a blood sample of approximately 5 mL for assessment of antibody responses to routine paediatric vaccines
- Collect and record breastfeeding information.

- Complete the participant's source documents.
- Record AEs as described in Section 13 and 14.
- Record non-study vaccines, any medication taken to treat AEs, and all concomitant medications (including herbal remedies and antibiotic medications).
- The investigator or an authorised designee completes the CRF.

11.2.6. HIV exposed infants

All HIV exposed infants will be followed up according to the Uganda Medical schedule including DNA PCR and prophylaxis with nevirapine syrup at the appropriate ages.

11.3. Unscheduled visits

If the participant reports redness or swelling at the injection site measuring ≥21 measuring device units (≥10.5 cm), fever ≥39.0°C (≥102.1°F), or severe injection site pain, severe nausea/vomiting, severe diarrhea, severe headache, severe fatigue/tiredness, severe muscle pain, or severe joint pain, a telephone contact must occur as soon as possible between the participant and the investigator or a medically qualified member of the study site staff to assess if an unscheduled visit is required. A site visit must be scheduled as soon as possible to assess the extent of the reaction unless:

- The participant is unable to attend the unscheduled visit.
- The reaction is no longer present at the time of the telephone contact.
- The participant recorded an incorrect value in the paper diary card (confirmation of a paper diary card data entry error).
- The investigator determined it was not needed.

This telephone contact will be recorded in the CRF and in the participant's source documentation.

If the participant is unable to attend the unscheduled visit, any ongoing reactions must be assessed at the next scheduled visit.

The reactions should be assessed by the investigator or a medically qualified member of the study staff such as a study physician or a study nurse, as applicable to the investigator's local practice, who will:

- Measure oral temperature.
- Measure minimum and maximum diameters of redness (if present).
- Measure minimum and maximum diameters of swelling (if present).
- Assess any injection site pain that is present in accordance with the grading scale provided in Section 13.2.
- Assess for lymphadenopathy associated with any present local reaction.
- Assess any systemic events (nausea/vomiting, diarrhoea, headache, fatigue, muscle pain, or joint pain) that are present in accordance with the grading scale provided in Section 13.2.

The investigator or an authorised designee will complete the unscheduled visit page of the CRF.

Participants will also be instructed to contact site staff if they experience any possible Grade 4 prompted systemic event (i.e., emergency room visit or hospitalisation for headache, fatigue, muscle pain, joint pain, etc.) within 7 days after vaccination. Study staff may contact the participant to obtain additional information on Grade 3 events entered into the paper diary card. Lastly, participants will be instructed to contact the site to report any significant illness, medical event, or hospitalisation that occurs during the study period. The site should determine if an unscheduled visit to further evaluate the event is warranted in all such cases.

11.4. Participant withdrawal

An investigator and/or sponsor can withdraw a participant from the study if deemed appropriate. In addition, if a participant fails to continue to meet the inclusion criteria, new

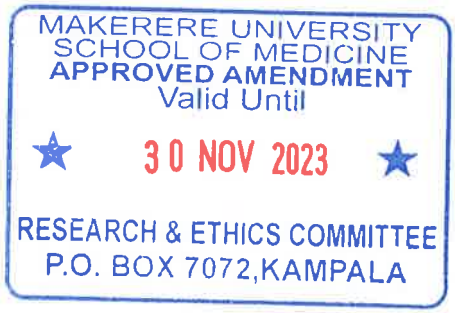
information becomes available that would exclude the participant, or the participant develops a condition or situation that would meet exclusion criteria, the participant may be considered for withdrawal. Infant participants born from vaccinated maternal participants may be considered for withdrawal from study procedures for any medical condition(s) that, in the opinion of the investigator, would contraindicate blood sampling.

Reasons why a participant may discontinue or be withdrawn from the study include, but are not limited to, failure to meet entrance criteria (screening failure), AE, death, protocol violation, lost to follow-up, no longer willing to participate in the study, study terminated by sponsor, investigator declined further study participation, or any other reason. Participants who have received the investigational product will not be replaced regardless of the reason for withdrawal.

11.5. Duration of treatment period and follow-up

Each mother-infant pair will be followed up from study enrolment at ≥ 27 0/7 weeks gestation until the infant is aged 365 days (+ 20 days).

To assess for any long-term adverse events, mothers and their infants will be screened for any SAE on every visit. On visit 5 and 8, participants will be followed-up with a phone call. All the phone numbers registered including the one for the Next of Kin will be called at least three times on three different days, in case a mother can't be easily reached.



Schedule of Activities for Maternal Participants										
Visit Number	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**
Visit Description	**Screening**	**Vaccination**	**2-Week Follow-up Visit (a)**	**1-Month Follow-up Visit (a)**	**Delivery**	**1-Week Postdeliv. Follow-up**	**6-Week Postdeliv. Follow-up**	**18-Week Postdeliv. Follow-up**	**6-Month Postdeliv. Follow-up**	**12-Month Postdeliv. Follow-up**
Visit Window (Days)	**Day -14 to Day -2 Prior to Day 1**	**Day 1**	**14-17 Days After Visit 1**	**28-42 Days After Visit 1**	**Varies**	**7-10 Days After Visit 4**	**35-49 Days After Visit 4**	**120-140 Days After Visit 4**	**160-200 Days After Visit 4**	**365-385 Days After Visit 4**
Type of Visit	**Clinic**	**Clinic**	**Clinic**	**Clinic**	**Hospital**	**Phone Call**	**Clinic**	**Clinic**	**Phone Call**	**Clinic**
Informed consent	X									
Demography	X									
Record current alcohol and tobacco usage	X									
Medical history including obstetric, gestational and immunisation history	X									
Record LMP and EDD	X									
Vital signs (b)	X	X	X	X						
Physical examination	X									

Schedule of Activities for Maternal Participants										
Visit Number	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**
Visit Description	**Screening**	**Vaccination**	**2-Week Follow-up Visit (a)**	**1-Month Follow-up Visit (a)**	**Delivery**	**1-Week Postdeliv. Follow-up**	**6-Week Postdeliv. Follow-up**	**18-Week Postdeliv. Follow-up**	**6-Month Postdeliv. Follow-up**	**12-Month Postdeliv. Follow-up**
Visit Window (Days)	**Day -14 to Day -2 Prior to Day 1**	**Day 1**	**14-17 Days After Visit 1**	**28-42 Days After Visit 1**	**Varies**	**7-10 Days After Visit 4**	**35-49 Days After Visit 4**	**120-140 Days After Visit 4**	**160-200 Days After Visit 4**	**365-385 Days After Visit 4**
Type of Visit	**Clinic**	**Clinic**	**Clinic**	**Clinic**	**Hospital**	**Phone Call**	**Clinic**	**Clinic**	**Phone Call**	**Clinic**
Targeted physical examination		X	X	X			X			
Obstetric examination	X	X	X	X						
Obstetric ultrasound	X									
Record non-study vaccine information	X	X	X	X	X					
Record concomitant medication	X	X	X	X	X	X	X	X	X	X
Record use of antibiotic medication	X	X	X	X	X	X	X	X	X	X
Review eligibility criteria	X									
Review screening laboratory results (c)		X								

Schedule of Activities for Maternal Participants										
Visit Number	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**
Visit Description	**Screening**	**Vaccination**	**2-Week Follow-up Visit (a)**	**1-Month Follow-up Visit (a)**	**Delivery**	**1-Week Postdeliv. Follow-up**	**6-Week Postdeliv. Follow-up**	**18-Week Postdeliv. Follow-up**	**6-Month Postdeliv. Follow-up**	**12-Month Postdeliv. Follow-up**
Visit Window (Days)	**Day -14 to Day -2 Prior to Day 1**	**Day 1**	**14-17 Days After Visit 1**	**28-42 Days After Visit 1**	**Varies**	**7-10 Days After Visit 4**	**35-49 Days After Visit 4**	**120-140 Days After Visit 4**	**160-200 Days After Visit 4**	**365-385 Days After Visit 4**
Type of Visit	**Clinic**	**Clinic**	**Clinic**	**Clinic**	**Hospital**	**Phone Call**	**Clinic**	**Clinic**	**Phone Call**	**Clinic**
Review temporary delay criteria		X								
Revlew continued eligibility		X	X	X	X	X	X	X	X	X
Record systemic events at baseline in the paper diary card		X								
Assign single participant identifier	X									
Assign participant randomisation and container number		X								

Schedule of Activities for Maternal Participants										
Visit Number	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**
Visit Description	**Screening**	**Vaccination**	**2-Week Follow-up Visit (a)**	**1-Month Follow-up Visit (a)**	**Delivery**	**1-Week Postdeliv. Follow-up**	**6-Week Postdeliv. Follow-up**	**18-Week Postdeliv. Follow-up**	**6-Month Postdeliv. Follow-up**	**12-Month Postdeliv. Follow-up**
Visit Window (Days)	**Day -14 to Day -2 Prior to Day 1**	**Day 1**	**14-17 Days After Visit 1**	**28-42 Days After Visit 1**	**Varies**	**7-10 Days After Visit 4**	**35-49 Days After Visit 4**	**120-140 Days After Visit 4**	**160-200 Days After Visit 4**	**365-385 Days After Visit 4**
Type of Visit	**Clinic**	**Clinic**	**Clinic**	**Clinic**	**Hospital**	**Phone Call**	**Clinic**	**Clinic**	**Phone Call**	**Clinic**
Blood draw for immunogenicity assessment (~10 mL per blood sample) (d)		X	X	X	X (e)		X			X
Breast milk collection					X (e)		X	X		
Administer investigational product		X								
Postvaccination observation (30 minutes) and assessment of immediate adverse events		X								

Schedule of Activities for Maternal Participants										
Visit Number	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**
Visit Description	**Screening**	**Vaccination**	**2-Week Follow-up Visit (a)**	**1-Month Follow-up Visit (a)**	**Delivery**	**1-Week Postdeliv. Follow-up**	**6-Week Postdeliv. Follow-up**	**18-Week Postdeliv. Follow-up**	**6-Month Postdeliv. Follow-up**	**12-Month Postdeliv. Follow-up**
Visit Window (Days)	**Day -14 to Day -2 Prior to Day 1**	**Day 1**	**14-17 Days After Visit 1**	**28-42 Days After Visit 1**	**Varies**	**7-10 Days After Visit 4**	**35-49 Days After Visit 4**	**120-140 Days After Visit 4**	**160-200 Days After Visit 4**	**365-385 Days After Visit 4**
Type of Visit	**Clinic**	**Clinic**	**Clinic**	**Clinic**	**Hospital**	**Phone Call**	**Clinic**	**Clinic**	**Phone Call**	**Clinic**
Dispense paper diary card, thermometer, and measuring device (f)		X								
Review and/or collect paper diary card		X	X							
Record pregnancy outcome information					X					
Record adverse events		X	X	X	X	X	X	X	X	X

Schedule of Activities for Maternal Participants										
Visit Number	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**
Visit Description	**Screening**	**Vaccination**	**2-Week Follow-up Visit (a)**	**1-Month Follow-up Visit (a)**	**Delivery**	**1-Week Postdeliv. Follow-up**	**6-Week Postdeliv. Follow-up**	**18-Week Postdeliv. Follow-up**	**6-Month Postdeliv. Follow-up**	**12-Month Postdeliv. Follow-up**
Visit Window (Days)	**Day -14 to Day -2 Prior to Day 1**	**Day 1**	**14-17 Days After Visit 1**	**28-42 Days After Visit 1**	**Varies**	**7-10 Days After Visit 4**	**35-49 Days After Visit 4**	**120-140 Days After Visit 4**	**160-200 Days After Visit 4**	**365-385 Days After Visit 4**
Type of Visit	**Clinic**	**Clinic**	**Clinic**	**Clinic**	**Hospital**	**Phone Call**	**Clinic**	**Clinic**	**Phone Call**	**Clinic**
Record medically attended adverse events and serious adverse events		X	X	X	X	X	X	X	X	X
1 rectal and 1 vaginal swab for GBS microbiological culture (g)		X			X (h)		X			
Blood draw for HBV, HCV, CBC, renal and liver function testing (~5 mL) (d)	X									

Schedule of Activities for Maternal Participants										
Visit Number	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**
Visit Description	**Screening**	**Vaccination**	**2-Week Follow-up Visit (a)**	**1-Month Follow-up Visit (a)**	**Delivery**	**1-Week Postdeliv. Follow-up**	**6-Week Postdeliv. Follow-up**	**18-Week Postdeliv. Follow-up**	**6-Month Postdeliv. Follow-up**	**12-Month Postdeliv. Follow-up**
Visit Window (Days)	**Day -14 to Day -2 Prior to Day 1**	**Day 1**	**14-17 Days After Visit 1**	**28-42 Days After Visit 1**	**Varies**	**7-10 Days After Visit 4**	**35-49 Days After Visit 4**	**120-140 Days After Visit 4**	**160-200 Days After Visit 4**	**365-385 Days After Visit 4**
Type of Visit	**Clinic**	**Clinic**	**Clinic**	**Clinic**	**Hospital**	**Phone Call**	**Clinic**	**Clinic**	**Phone Call**	**Clinic**
Blood draw for CBC, HIV, and syphilis testing (~5 mL) (d)										
Blood draw for CD4 count, viral load (~5 mL) (d)		X								
Urine sample for glucose and protein testing	X	X								
Urine pregnancy test (i)								X		X
Complete the participant's source documents and CRF	X	X	X	X	X	X	X	X	X	X

Table 1

A placebo controlled clinical trial investigating the safety and immunogenicity of GBS6 in pregnant women with and without human immunodeficiency virus (HIV) infection and their infants

Abbreviations: EDD = estimated date of delivery; paper diary card = electronic diary; GBS = group B streptococcus; HBV = hepatitis B virus; HCV = hepatitis C virus; HIV = human immunodeficiency virus; LMP = last menstrual period; Postdeliv. = postdelivery; Vacc. = vaccination; CBC – complete blood count.

a. Visits at 2 weeks and 1 month after vaccination will not be performed if delivery occurs before the visits. Once delivery occurs, the visit windows are calculated based on delivery date.

b. Vital signs include weight, height (only required at Visit 0), oral temperature, sitting blood pressure and pulse rate, and respiratory rate.

c. If abnormal laboratory tests are reported at Visit 0 and the investigator believes the results to be erroneous, the abnormal laboratory parameters may be retested.

d. All blood volumes are approximate.

e. Sample may be collected up to 72 hours after delivery.

f. Participants will provide (in a paper diary card) a baseline assessment of prompted systemic events prior to vaccination and participants will record (in a paper diary card) reactogenicity events each evening for 7 days following vaccination. Remind participants that study staff may contact them to obtain additional information on Grade 3 events entered into the paper diary card. Ask participants to contact the investigator or site staff immediately if they are prompted by the paper diary card from Day 1 to Day 7 following vaccination to determine if an unscheduled visit is required.

g. Prior to vaccination, 2 swabs will be collected during the clinic visit from the following sites: 1 rectal and 1 vaginal.

h. Rectal/vaginal swabs may be collected from onset of labour up to 72 hours after delivery.

i. Any participant found to be pregnant during the study will be followed up to outcome of the pregnancy.

Schedule of Activities for Infant Participants						
Visit Number	**1**	**2**	**3**	**4**	**5**	**6**
Equivalent Visit Number for Maternal Participants	**4**	**5**	**6**	**7**	**8**	**9**
Visit Description	**Delivery**	**1-Week Postdelivery Follow-up**	**6-Week Postdelivery Follow-up**	**18-Week Postdelivery Follow-up**	**6-Month Postdelivery Follow-up**	**12-Month Postdelivery Follow-up**
Visit Window (Days)	**Varies**	**7-10 Days After Visit 1**	**35-49 Days After Visit 1**	**120-140 Days After Visit 1**	**160-200 Days After Visit 1**	**365-385 Days After Visit 1**
Type of Visit	**Hospital**	**Phone Call**	**Clinic**	**Clinic**	**Phone Call**	**Clinic**
Assign single participant identifier	X					
Collect demography and birth information (including Ballard score)	X					
Vital signs (a)	X		X	X		X
Physical examination	X		X	X		X
Developmental assessment (Ages and Stages questionnaire)						X
Record concomitant medication	X	X	X	X	X	X
Record use of antibiotic medication	X	X	X	X	X	X
Record non-study vaccine information	X	X	X	X	X	X
Review continued eligibility	X	X	X	X	X	X
Record breastfeeding information	X	X	X	X	X	X
Blood draw (~5 mL per blood sample) (b)			X	X		X
Cord blood sample (c) (~10 mL) (b) for immunogenicity assessment	X					

Schedule of Activities for Infant Participants						
Visit Number	**1**	**2**	**3**	**4**	**5**	**6**
Equivalent Visit Number for Maternal Participants	**4**	**5**	**6**	**7**	**8**	**9**
Visit Description	**Delivery**	**1-Week Postdelivery Follow-up**	**6-Week Postdelivery Follow-up**	**18-Week Postdelivery Follow-up**	**6-Month Postdelivery Follow-up**	**12-Month Postdelivery Follow-up**
Visit Window (Days)	**Varies**	**7-10 Days After Visit 1**	**35-49 Days After Visit 1**	**120-140 Days After Visit 1**	**160-200 Days After Visit 1**	**365-385 Days After Visit 1**
Type of Visit	**Hospital**	**Phone Call**	**Clinic**	**Clinic**	**Phone Call**	**Clinic**
Blood spot card collection (d)	X					
Record adverse events	X	X	X	X	X	X
Nasal/rectal swabs for GBS microbiological culture (e)	X		X	X		
Record medically attended adverse events, serious adverse events, and adverse events of special interest	X	X	X	X	X	X
Complete the participant's source documents and CRF	X	X	X	X	X	X

Table 2; Abbreviations: GBS = group B streptococcus; N/A = not applicable.

a. Vital signs include weight, height (length at Visit 1), head circumference, axillary temperature, pulse rate, and respiratory rate.
b. All blood volumes are approximate.
c. If cord blood is unavailable, then a 2.5-mL blood sample may be collected in the infant participants up to 72 hours after delivery.
d. One blood spot card collection will be performed using cord blood sample, and a second performed using a heel prick. A single blood spot card will be collected using blood draw (up to 72 hours after delivery) if cord blood unavailable.
e. Two swabs will be collected during the clinic visit from the following sites: 1 nasal and 1 rectal.

12. Assessments

12.1. Biological Samples

Blood, breastmilk and swab samples will be used only for scientific research. Each sample will be labeled with a code so that the laboratory personnel testing the samples will not know the participant's identity. Unless a time limitation is required by local regulations or ethical requirements, the samples will be stored for up to 15 years after the end of the study and then destroyed. If allowed by the ICD, stored samples may be used for additional testing to better understand the immune responses to the vaccine(s), to inform the development of other products, and/or for vaccine related assay work supporting vaccine programs. No testing of the participant's genetic material will be performed.

The participant (participant's parent) may request that her samples (child's samples), if still identifiable, be destroyed at any time; however, any data already collected from those samples will still be used for this research. The biological samples may be shared with other researchers as long as confidentiality is maintained and no testing of the participant's genetic material is performed. Screening blood tests (HIV, HBV/HCV, syphilis, CBC, renal and liver function) as well as CD4 counts and viral load will be undertaken by Infectious Diseases Institute laboratories, Kampala, Uganda.

12.2. Immunogenicity

Immunology samples will be processed and stored at Makerere University-Clinical Microbiology Laboratory, in Kampala, Uganda and analysed by St George's University Laboratory (SGUL), in London, UK. Analysis of GBS serotypespecific IgG titres will be done by DLIA (Luminex-based multi-plex direct immunoassay). Functional antibody will be measured by opsonophagocytic killing assay (OPkA) at SGUL.

12.3. GBS antibody testing

Sera collected from maternal participants throughout the study and from infant participants will be assayed for GBS6 serotype specific anti-capsular antibodies. Sample collection, processing, storage, and shipping information can be found in the study SOP or equivalent manual. OPA results will be reported as OPA titers. Concentrations of anti-capsular IgG for the 6 serotypes (Ia, Ib, II, III, IV, and V) will be determined in all participants for each blood sample by direct Luminex immunoassay (dLIA) and reported as IgG concentrations. Concentrations of anti-capsular IgG for the 6 serotypes (Ia, Ib, II, III, IV, and V) may be determined in samples eluted from dried blood spots taken at birth from infant participants as part of exploratory analyses. In addition, other isotypes and subtypes may be measured for exploratory analyses.

12.4. Development of Serological assays and reagents

Any sera remaining after completion of the planned immunologic assays from blood draws taken throughout the study in nonpregnant women, maternal participants, and infant participants may be used for assay development and standardisation. This would include use of the sera in assay validation and the development of control panels of sera with different levels of antibody. This work is critical in the development and validation of serologic assays that is required by regulatory authorities for their use in the licensure of a vaccine.

12.5. Assessment of antibody responses to routine paediatric vaccines in infant participants

Sera from the 18week and 12month blood draws in infant participants will be assayed for antibodies to PCV 13 and diphtheria-containing vaccines. Serotype specific anti-capsular antibodies to the 13 serotypes in PCV 13 will be measured by dLIA. Diphtheria antibodies will be measured by standardised Luminex assay. Antibodies against the other vaccines

given as part of the National Programme for Immunisation may also be tested using validated assays at St George's University Laboratory (SGUL), in London, UK.

12.6. GBS Microbiological Cultures

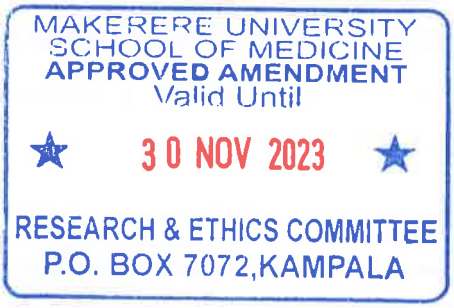
One rectal and one vaginal swab will be collected from maternal participants at Day 1 (Visit 1), at delivery (Visit 4), and 6 weeks after delivery (Visit 6), and oral and rectal swabs will be obtained from their infant participants at birth and at 6 weeks (Visit 3) and 18 weeks (Visit 7) of age and cultured for GBS, to assess colonisation status.

Swab samples collected will be sent to Makerere University-Clinical Microbiology Laboratory, in Kampala, Uganda for GBS identification.

12.7. Future use of stored specimen

Samples may be used for future testing not specified in this proposal. Although no excess sample is expected to be obtained during the study, any leftovers would be stored to test for additional immunological responses that turn out to be important as a result of ongoing research. Additional consent will be obtained to have the samples stored for future use at the time of recruitment.

Additional future research to be done in keeping with the UNCST guidelines.



13. Safety parameters

Safety parameters will be assessed as described in the schedule of activities, Section 11, and below.

A medical history and physical examination will be performed on all participants, to establish a baseline. Significant medical history and observations from the physical examination will be documented in the CRF.

The safety parameters include paper diary card reports of local reactions and systemic events that occur in the 7 days after investigational product administration. These prospectively collected occurrences of local reactions and systemic events are graded as described in Section 13.8

Acute reactions within the first 30 minutes after investigational product administration will be assessed and documented in the AE CRF.

In addition, AEs, MAEs, and SAEs are collected, recorded, and reported as defined in Section 14.

13.1 Participant paper diary card

The responsible research nurse/clinician will be asked to monitor and record local reactions reported by the participant, as well as, systemic events, including fever, and antipyretics/pain medication used to prevent and/or treat symptoms, within a fixed time window each day for 7 days following vaccination (where Day 1 is the day of vaccination) on a system that uses a personal digital assistant (PDA) or other technology. A baseline assessment (nausea/vomiting, diarrhea, headache, fatigue/tiredness, muscle pain, or joint pain over the previous month) prior to vaccination will be recorded in the paper diary card. This system, hereafter referred to as the participant's paper diary card, allows recording of these assessments only within a fixed time window, thus providing the accurate representation of the participant's experience at that time. Data on local reactions, systemic

events, and antipyretics/pain medication used to prevent and/or treat symptoms reported on the paper diary card will be uploaded manually entered into REDCap, where they will be available for review by investigators, their qualified designees, and sponsor staff at all times via an internet-based portal. At intervals agreed to by the sponsor, these data will be transferred electronically for analysis and reporting. These data do not need to be reported by the investigator in the CRF. However, if a participant withdraws because of prompted events reported in the paper diary card, the event(s) should be recorded on the AE page of the CRF, regardless of whether the investigator considers the event(s) to be clinically significant.

Investigators (or appropriately qualified designee) are required to review the paper diary card data online to evaluate participant compliance and as part of the ongoing safety review.

The investigator or designee must contact the participant in order to obtain stop dates for any reactions ongoing on the last day that the paper diary card was completed. The stop dates should be documented in the source documents and the information entered in the CRF.

13.2 Grading Scale for prompted events

The grading scales used in this study to assess AEs as described below are based on concepts outlined in the Food and Drug Administration (FDA) Center for Biologics Evaluation and Research (CBER) guidelines on toxicity grading scales for healthy adult volunteers enrolled in preventive vaccine clinical trials.

13.2.1 Local reactions

From Day 1 to Day 7, where Day 1 is the day of vaccination, participants will be asked to assess pain at the injection site, redness, and swelling and to record the symptoms in the paper diary card in the evening. Redness and swelling will be measured and recorded in measuring device units (range: 1 to 21+), and then categorised during analysis as mild,

moderate, or severe based on the grading scale in Table 3 below. Measuring device units can be converted to centimeters according to the following scale: 1 measuring device unit = 0.5 cm. Pain at the vaccine injection site will be assessed by the participant as mild, moderate, or severe according to the grading scale in Table 3 below. A participant with a severe (Grade 3 or above) local reaction will be prompted to contact the investigator to perform an unscheduled visit and assess the reaction.

Only an investigator is able to classify a participant's local reaction as Grade 4, after physical examination of the participant or documentation from another medically qualified source (e.g., emergency room or hospital record), or, in the case of pain at the injection site only, telephone contact with the participant. If a participant experiences a Grade 4 local reaction, the investigator must immediately notify the sponsor. Site staff will educate the participant regarding signs and symptoms that would prompt site contact. The procedure for notification of the sponsor is provided in the study documentation.

If a local reaction persists beyond the end of the paper diary card period following vaccination, the participant will be requested to report that information and/or any new AEs that develop to the investigator. The investigator will enter this additional information in the CRF.

Table 3. Local Reaction Grading Scale

	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Grade 4
Pain at injection site	Does not interfere with activity	Repeated use of nonnarcotic pain reliever >24 hours or interferes with activity	Any use of narcotic pain reliever or prevents daily activity	Emergency room visit or hospitalisation

Table 3. Local Reaction Grading Scale

	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Grade 4
Erythema/ Redness	2.5 cm to 5.0 cm (5 to 10 measuring device units)	>5.0 cm to 10.0 cm (11 to 20 measuring device units)	>10 cm (≥21 measuring device units)	Necrosis or exfoliative dermatitis
Induration/ Swelling	2.5 cm to 5.0 cm (5 to 10 measuring device units)	>5.0 cm to 10.0 cm (11 to 20 measuring device units)	>10 cm (≥21 measuring device units)	Necrosis

a. Participants experiencing ≥ Grade 3 local reactions are to be seen by the study site.

b. Grade 4 assessment should be made by the investigator. Grade 4 will not be collected in the electronic diary but will be recorded as an AE on the case report form.

c. Prevents daily activity, i.e., results in missed days of work or school or is otherwise incapacitating, or includes use of narcotics for analgesia.

13.2.2 Systemic events

From Day 1 to Day 7, where Day 1 is the day of vaccination, participants will be asked to assess nausea/vomiting, diarrhea, headache, fatigue/tiredness, muscle pain, and joint pain and to record the symptoms in the paper diary card in the evening. The symptoms will be assessed by the participant as mild, moderate, or severe according to the grading scale in Table 4 below. Participants will also be instructed to contact site staff if they experience any possible Grade 4 prompted systemic event (i.e., emergency room visit or hospitalisation for nausea/vomiting, diarrhea, headache, fatigue/tiredness, muscle pain, or joint pain) within 7 days after vaccination. Study staff may also contact the participant to obtain additional information on Grade 3 events entered into the paper diary card.

Only an investigator is able to classify a participant's systemic event as Grade 4, after physical examination of the participant or documentation from another medically qualified source (e.g., emergency room or hospital record) or telephone contact with the participant.

If a participant experience a Grade 4 systemic event, the investigator must immediately notify the sponsor. The procedure for notification of the sponsor is provided in the study documentation.

Further, if a systemic event persists beyond the end of the paper diary card period following vaccination, the participant will be requested to report that information and/or any new AEs that develop to the investigator. The investigator will enter this additional information in the CRF.

Table 4. Systemic Event Grading Scale

	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Grade 4
Nausea/Vomiting	No interference with activity or 1-2 times in 24 hours	Some interference with activity or >2 times in 24 hours	Prevents daily activity, requires IV hydration	Emergency room visit or hospitalisation for hypotensive shock
Diarrhea	2-3 loose stools in 24 hours	4-5 loose stools in 24 hours	≥6 loose stools in 24 hours	Emergency room visit or hospitalisation
Headache	No interference with activity	Repeated use of nonnarcotic pain reliever >24 hours or some interference with activity	Significant; any use of narcotic pain reliever or prevents daily activity	Emergency room visit or hospitalisation
Fatigue/Tiredness	No interference with activity	Some interference with activity	Significant; prevents daily activity	Emergency room visit or hospitalisation

Table 4. Systemic Event Grading Scale

	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Grade 4
Muscle pain	No interference with activity	Some interference with activity	Significant; prevents daily activity	Emergency room visit or hospitalisation
Joint pain	No interference with activity	Some interference with activity	Significant; prevents daily activity	Emergency room visit or hospitalisation

Abbreviation: IV = intravenous.

a. Participants experiencing ≥ Grade 3 systemic events are to be seen by the study site.

b. Grade 4 assessment should be made by the investigator. Grade 4 will not be collected in the electronic diary but will be collected as an AE on the case report form.

c. Prevents daily routine activity, i.e., results in missed days of work or school or is otherwise incapacitating, or includes use of narcotics for analgesia.

13.2.3 Fever

In order to record information on fever, a digital thermometer will be given to the participant with instructions on how to measure oral temperature at home. Temperature will be collected in the evening daily for 7 days following vaccination (where Day 1 is the day of vaccination) and at any time during the 7 days that fever is suspected. Fever is defined as an oral temperature of ≥38.0°C (≥100.4°F). The highest temperature for each day will be recorded in the paper diary card. In the event of a fever on Day 7, temperature will be collected daily until fever has resolved (1 day of temperature less than 38.0°C [100.4°F] in order to collect a stop date in the CRF). A participant with a fever >40.0°C (>104.0°F) will be prompted to contact the investigator to assess the fever and perform an unscheduled visit as appropriate. Study staff must also contact the participant to obtain additional information if a temperature of ≥39°C (≥102.1°F) is entered into a paper diary card.

Temperature will be measured and recorded to 1 decimal place and then grouped into ranges for the analysis according to Table 5 below.

Table 5. Ranges for Fever

38.0°C to 38.4°C (100.4°F to 101.1°F)
>38.4°C to 38.9°C (101.2°F to 102.0°F)
>38.9°C to 40.0°C (102.1°F to 104.0°F)
>40.0°C (>104.0°F)

13.3. Other safety monitoring

Adverse events and serious adverse events reported outside of the paper diary card are recorded and reported as described in Section 14.

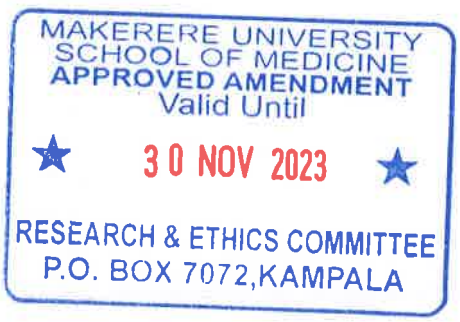
14. Adverse event reporting

For maternal immunisation- clinical studies conducted in pregnant women, data on the exposure during pregnancy (EDP) as well as pregnancy outcome are collected and analysed in the clinical database. For these studies, in general, EDP cases are not reportable unless associated with SAEs/nonserious AEs.

14.1. Requirements

For all AEs, the investigator will pursue and obtain information adequate both to determine the outcome of the AE and to assess whether it meets the criteria for classification as a serious adverse event (SAE) requiring immediate notification to the Makerere University School of Medicine Research and Ethics Committee (SOMREC), Data and Safety Monitoring Board (DSMB), sponsor (SGUL), Uganda National Council for Science and Technology (UNCST) and Pfizer Safety. SAEs shall be reported for the entire duration of the study. Should an investigator be made aware of any SAE occurring any time after the active reporting period, this will be promptly reported.

The table below summarises the requirements for recording safety events on the CRF and for reporting safety events on the Clinical Trial (CT) Serious Adverse Event (SAE) Report Form. These requirements are delineated for the following events: SAEs; non-serious AEs; and occupational exposure.



Safety Event	Recorded on the CRF	Reported on the CT SAE Report Form Within 24 Hours of Awareness
Maternal and Infant participants		
SAE	All	All
Nonserious AE	All	None
Exposure to the investigational product under study via occupational exposure	None	Occupational exposure (regardless of whether associated with an AE)

The PI/Designee will coordinate the safety monitoring and reporting in the study. SAEs will be reported to SOMREC following local law and requirements. SAEs will be reported to the

DSMB as required as well. A detailed description of DSMB functions and responsibilities and guidelines on the transmission flow of SAEs is provided in the DSMB charter. Notification of SAE to concerned National Regulatory Authorities will follow national law requirements. The table below summarizes SAE reporting timelines.

SAE reporting timelines

Reported To	Reported By	Timeline
Sponsor	PI (or designee)	Within 24 hours for all SAEs
Pfizer Safety	PI (or designee)	Within 24 hours for all SAEs
Local IRB	PI (or designee)	As soon as possible but not later than 7 days for all SAEs
Uganda National Drug Authority (NOA)	PI (or designee)	As soon as possible but not later than 7 days for all SAEs
DSMB	Sponsor (or designee)	Within 24 hours for fatal and life threatening events or SUSARs, and within 7 days for other SUSARs (according to DSMB charter)

This time frame also applies to additional new (follow up) information on previously forwarded reports. All SAEs will be monitored

14.2. Additional details on recording adverse events on the CRF

All events detailed in the table above will be recorded on the AE page(s) of the CRF. It should be noted that the CT SAE Report Form for reporting of SAE information is not the same as the AE page of the CRF. When the same data are collected, the forms must be completed in a consistent manner. AEs should be recorded using concise medical terminology and the same AE term should be used on both the CRF and the CT SAE Report Form for reporting of SAE information.

14.3. Eliciting Adverse event information

The investigator is to record on the CRF all directly observed AEs and all AEs spontaneously reported by the study participant/parent(s). In addition, each study participant/parent(s) will be questioned about the occurrence of AEs in a nonleading manner.

14.4. Withdrawal from the study due to Adverse events

Withdrawal due to AEs should be distinguished from withdrawal due to other causes, according to the definition of AE noted below, and recorded on the CRF.

When a participant withdraws from the study because of an SAE, the SAE must be recorded on the CRF and reported, as appropriate, on the CT SAE Report Form, in accordance with the Section 14.1, above.

14.5. Time period for collecting AE/SAE information

The period of observation for adverse events extends from the time the study participant receives vaccination until she undergoes the final study examination. Any medical event that occurs after the informed consent form is signed, but prior to being vaccinated and is related to a study procedure, will be documented as an adverse event and recorded on the Adverse Events CRF. Any medical event that occurs after the informed consent form is signed, but prior to being vaccinated and is not related to a study procedure, will be documented as a pre-existing condition and will be recorded on the Medical History CRF. A complete medical history will be noted and physical examination will be performed on all participant before enrolment. The CRFs will capture the medical history and findings of physical examination done at enrolment to establish a baseline. All adverse events, regardless of severity, will be monitored by the investigator until resolution. All participants experiencing adverse events - whether considered associated with the use of the study vaccine or not will be monitored until symptoms subside and any abnormal laboratory values have returned to baseline, or until there is a satisfactory explanation for the changes

observed, or until death, in which case a full pathologist's report should be supplied, if possible.

14.5.1 Maternal participants

In this study, the investigator and site staff will ensure the active elicitation and collection of AEs and SAEs through Visit 4. At all subsequent visits (Visits 5 to 9), only MAEs and SAEs, including hospitalisations, will be reported. Immediate AEs will be reported as described in section 13.9.3. In addition, AEs occurring up to 48 hours after the Visit 4, Visit 6 and Visit 9 blood draws that are related to study procedures must be reported in the CRF.

14.5.2 Infant participants

The investigator and site staff will ensure the active elicitation and collection of AEs and SAEs from birth (Infant Visit 1) through Infant Visit 3. At subsequent visits (Visit 4, Visit 5, and Visit 6), only AEs of special interest, MAEs, and SAEs, including hospitalisations, will be reported. In addition, AEs occurring up to 48 hours after the Visit 4 and 6 blood draws that are related to study procedures must be reported in the CRF. In addition, AEs occurring up to 48 hours after the Visit 4 nasal and rectal swab samples that are related to study procedures must be reported in the CRF.

14.5.3 Recording non-serious AEs and SAEs on the CRF

All AEs/SAEs occurring in a participant during the active collection period are recorded in the CRF.

Follow up by the investigator may be required until the event or its sequelae resolve or stabilise at a level acceptable to the investigator, the sponsor and regulatory authorities.

The investigator obtains general information on the pregnancy and its outcome for all study participants. The investigator will follow the pregnancy until completion (or until pregnancy termination). In the case of a live birth, the structural integrity of the neonate can be assessed at the time of birth. In the event of a termination, the reason(s) for termination

should be specified and, if clinically possible, the structural integrity of the terminated fetus should be assessed by gross visual inspection (unless pre-procedure test findings are conclusive for a congenital anomaly and the findings are reported).

If the outcome of the pregnancy meets the criteria for an SAE (i.e., ectopic pregnancy, spontaneous abortion, including miscarriage and missed abortion, intrauterine fetal demise, neonatal death [defined as those deaths that occur within 1 month of birth], or congenital anomaly [in a live-born baby, a terminated fetus, an intrauterine fetal demise, or a neonatal death]), the investigator should record this information in the CRF. In addition, infant deaths after 1 month of age should be recorded in the CRF as SAEs.

14.6. Causality assessment

The degree of certainty with which an AE/SAE can be attributed to administration of the study vaccines (or alternative causes, e.g. natural history of the underlying diseases, concomitant therapy, etc.) will be determined by how well the event can be understood in terms of one or more of the following:

- Reaction of similar nature having previously been observed with this vaccine or type of vaccine and/or formulation.
- The event having often been reported in literature for similar types of vaccines.
- The event being temporally associated with vaccination or reproduced on re vaccination.

The Principal Investigator will assess the causality of all AE/SAEs, using the following question: "Is there a reasonable possibility that the AE/SAE may have been caused by the study vaccine(s)?" After assessment of causality, the AE/SAE will be categorized as related or unrelated, as defined below.

Related: there is suspicion that there is a relationship between vaccine and SAE (without determining the extent of probability); there is a reasonable possibility that the vaccine contributed to the SAE. All SAEs assessed as possibly, probably or definitely related to the vaccine

will be considered related to the study product.

Unrelated: there is no suspicion that there is a relationship between vaccine and SAE, there are other more likely causes and administration of the study vaccine is not suspected to have contributed to the SAE. All SAEs assessed as unrelated or doubtfully related to the vaccine will be considered unrelated to the study product.

When assessing AEs/SAEs, the below degree to which an AE/SAE can be attributed to the study vaccines will be used.

Not related: an AE not related to the use of study vaccine

Doubtfully: An AE for which an alternative explanation is more likely e.g. con meds/disease or the relationship in time suggests that a causal relationship is unlikely

Possibly: An AE that might be due to the use of study vaccine. An alternative explanation e.g. con meds/disease is inconclusive. The relationship in time is reasonable, therefore, the causal relationship cannot be excluded.

Probably: An AE that might be due to the use of study vaccine. The relationship in time is suggestive (e.g. confirmed by de-challenge). An alternative explanation e.g. con meds/disease is less likely.

Definitely: An AE that is listed as a possible adverse reaction and cannot be reasonably explained by an alternative explanation e.g. con meds/diseases. The relationship in time is very suggestive (e.g. it is confirmed by de challenge and re-challenge)

14.7. Definition of AE

An adverse event (AE) is defined as any untoward medical occurrence in a subject or clinical investigation subject administered a pharmaceutical product at any dose that does not necessarily have to have a causal relationship with this treatment. An AE can, therefore, be any unfavorable and unintended sign (including an abnormal laboratory finding, for example),

symptom, or disease temporally associated with the use of an investigational product, whether or not considered related to the investigational product. This definition includes intercurrent illnesses or injuries and exacerbation of pre-existing conditions. An unexpected adverse event is one that is not listed in the investigators brochure or current summary of product characteristics or an event that is by nature more specific or more severe than a listed event.

14.7.1 Grading of AEs

Grading of AEs will be undertaken using the criteria below (based on the 2017 DAIDS table)

Grade 1 Mild	asymptomatic or mild symptoms; no or minimal interference with usual social & functional activities, intervention not indicated
Grade 2 Moderate	moderate symptoms causing greater than minimal interference with usual social & functional activities, intervention indicated
Grade 3 Severe	severe symptoms causing inability to perform usual social & functional activities with intervention or hospitalization indicated
Grade 4 Potentially Life-threatening	symptoms causing inability to perform basic self care functions with intervention indicated to prevent permanent impairment, persistent disability or death
Grade 5	Death

14.8. Definition of Serious Adverse Events (SAEs):

An adverse event or suspected adverse reaction is considered "serious" if, in the view of either the investigator or sponsor, it results in any of the following outcomes:

- Life threatening adverse event
- Inpatient hospitalization or prolongation of existing hospitalization

• Persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions

• Congenital anomaly/birth defect

• Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

• Death

If the outcome of the pregnancy meets the criteria for an SAE (i.e., ectopic pregnancy, spontaneous abortion, including miscarriage and missed abortion, intrauterine fetal demise, neonatal death [defined as those deaths that occur within 1 month of birth], or congenital anomaly [defined as structural or functional anomalies (e.g., metabolic disorders) that occur during intrauterine life and can be identified prenatally, at birth or later in life]). These SAEs can occur in a live-born baby, a terminated fetus, an intrauterine fetal demise, or a neonatal death; the investigator should follow the procedures for reporting SAEs and record this information in the CRF. In addition, any infant death after 1 month of age should be reported as an SAE if the investigator assesses the infant death as related or possibly related to exposure to the investigational product.

Further follow-up may be requested by the sponsor and will be handled on a case-by-case basis (e.g., follow-up on preterm infant participants to identify developmental delays). SAEs occurring in a participant after the active collection period has ended are reported if the investigator becomes aware of them; at a minimum, all SAEs that the investigator believes have at least a reasonable possibility of being related to investigational product must be reported.

The same is applied for those SAEs after the active collection period has ended should they occur to the fetus. In addition, infant deaths that occur after 12 months of age should be reported as SAEs when the investigator believes the death has at least a reasonable possibility of being related to investigational product.

Adverse events which do not fall into these categories are defined as non-serious. It should be noted that a severe adverse event need not be serious in nature and that a serious adverse event need not, by definition, be severe.

14.9. Definition of Immediate Adverse events

Immediate AEs, defined as AEs occurring within the first 30 minutes after investigational product administration, will be assessed and documented in the AE CRF. The time of onset will be recorded for any AEs that occur on the same day as investigational product administration.

14.10. Definition of Medically attended Adverse events

An MAE is defined as a non-serious AE that results in an evaluation at a medical facility. MAEs will be assessed from screening for all participants up to Visit 9 for maternal participants and up to Visit 6 for infant participants.

14.11. Definition of Adverse events of special interest

Developmental delay, major congenital disorders, and suspected or confirmed GBS disease in infant participants will be reported from delivery through the end of the study (12-month postdelivery visit).

14.12. Routine medical facility visits and elective hospitalisation not associated with adverse events

Routine visits to medical facilities and elective hospitalisations not associated with an AE (i.e., healthcare visits for preventive care, or for routine physical examinations) will not be collected.

14.13. Definition of Hospitalisation

Hospitalisation is defined as any initial admission (even less than 24 hours) in a hospital or equivalent healthcare facility, or any prolongation of an existing admission. Admission also includes transfer within the hospital to an acute/intensive care unit (e.g., from the psychiatric wing to a medical floor, medical floor to a coronary care unit, or neurological floor to a tuberculosis unit). An emergency room visit does not necessarily constitute a hospitalisation; however, the event leading to the emergency room visit is assessed for medical importance.

Hospitalisation does not include the following:

- Rehabilitation facilities;
- Hospice facilities;
- Respite care (e.g., caregiver relief);
- Skilled nursing facilities;
- Nursing homes;
- Same-day surgeries (as outpatient/same-day/ambulatory procedures).

Hospitalisation or prolongation of hospitalisation in the absence of a precipitating clinical AE is not in itself an SAE. Examples include:

- Admission for treatment of a pre-existing condition not associated with the development of a new AE or with a worsening of the pre-existing condition (e.g., for workup of a persistent pre-treatment laboratory abnormality);
- Social admission (e.g., participant has no place to sleep);
- Administrative admission (e.g., for yearly physical examination);
- Protocol-specified admission during a study (e.g., for a procedure required by the study protocol);
- Optional admission not associated with a precipitating clinical AE (e.g., for elective cosmetic surgery);
- Hospitalisation for observation without a medical AE;
- Pre-planned treatments or surgical procedures, including vaginal delivery procedures and caesarean deliveries. These should be noted in the baseline documentation for the entire protocol and/or for the individual participant.

Diagnostic and therapeutic noninvasive and invasive procedures, such as surgery, should not be reported as SAEs. However, the medical condition for which the procedure was performed should be reported if it meets the definition of an SAE. For example, an acute appendicitis that begins during the reporting period should be reported if the SAE requirements are met, and the resulting appendectomy should be recorded as treatment of the AE.

For pregnant study participants hospitalization at less than 37 weeks (gestational age) will be classified as an AE related hospitalization. Please note that hospitalizations at >37 weeks for normal labour are not regarded as AE.

14.14. Exposure Medication Errors

Other exposures to the investigational product under study may occur in clinical trial settings, such as medication errors.

Safety Event	Recorded on the CRF	Reported on the CT SAE Report Form to Pfizer Safety Within 24 Hours of Awareness
Medication errors	All (regardless of whether associated with an AE)	Only if associated with an SAE

Medication errors may result from the administration or consumption of the investigational product by the wrong participant, or at the wrong time, or at the wrong dosage strength.

Medication errors include:

- Medication errors involving participant exposure to the investigational product;
- Potential medication errors or uses outside of what is foreseen in the protocol that do or do not involve the participating participant.

Other examples include, but are not limited to:

- The administration of expired investigational product;
- The administration of an incorrect investigational product;
- The administration of an incorrect dosage;
- The administration of investigational product that has undergone temperature excursion from the specified storage range, unless it is determined by the sponsor that the investigational product under question is acceptable for use.

Such medication errors occurring to a study participant are to be captured on the medication error page of the CRF, which is a specific version of the AE page.

In the event of a medication dosing error, the sponsor should be notified immediately.

Whether or not the medication error is accompanied by an AE, as determined by the investigator, the medication error is recorded on the medication error page of the CRF and,

if applicable, any associated AE(s), serious and nonserious, are recorded on an AE page of the CRF.

Medication errors should be reported to Pfizer Safety within 24 hours on a CT SAE Report Form only when associated with an SAE.

14.14.1 Occupational Exposure

An occupational exposure occurs when, during the performance of job duties, a person (whether a healthcare professional or otherwise) gets in unplanned direct contact with the product, which may or may not lead to the occurrence of an AE.

An occupational exposure is reported to Pfizer Safety within 24 hours of the investigator's awareness, using the CT SAE Report Form, regardless of whether there is an associated SAE. Since the information does not pertain to a subject enrolled in the study, the information is not recorded on a CRF; however, a copy of the completed CT SAE Report Form is maintained in the investigator site file.

14.14.2. New/Subsequent pregnancy exposure during the study

A new/subsequent pregnancy during the course of the study is reportable to Pfizer and the study sponsor within 24 hours of the investigator's awareness, using the SAE Reporting form and the exposure during pregnancy supplemental form (EDP) regardless of whether there is an associated SAE. In the event of an EDP form, the report should include the anticipated date of delivery.

Follow-up is conducted to obtain general information on the pregnancy and its outcome for all EDP reports with an unknown outcome. The investigator will follow the pregnancy until completion or until pregnancy termination and notify Pfizer, the sponsor and the necessary regulatory authorities of the outcome as a follow up to the initial EDP form.

14.14.3 Exposure During Breastfeeding

Exposure during breastfeeding reports are not expected for maternal subjects who breast-feed a child delivered during the study.

Scenarios of exposure during breastfeeding must be reported, irrespective of the presence of an associated SAE, within 24 hours of the investigator's awareness, using the CT SAE Report Form. An exposure during breastfeeding report is not created when a drug specifically approved for use in breastfeeding women (eg, vitamins) is administered in accord with authorized use. However, if the infant subject experiences an SAE associated with such a drug's administration, the SAE is reported together with the exposure during breastfeeding.

15. Ethical Considerations

15.1. Participant Recruitment process

Participant recruitment at a site will only commence once evidence of the following approval/essential documents are in place:

1. SOMREC approval
2. Kawempe National Referral Hospital's administrative clearance.
3. Kampala Capital City Authority administrative Clearance.
4. UNCST approval
5. NDA approval
6. St George's, University of London ethics committee approval
7. Biological Committee for Vaccines in Uganda
8. Final sponsorship Permission

15.2. Recruitment

Women will be recruited after 20 weeks gestation at antenatal clinic at Kawempe National Referral Hospital, Kawaala or Komamboga Health Centre III, Wakiso or Kisenyi Health Centre IV, following an ultrasound dating scan confirming a low risk, singleton pregnancy and a confirmatory HIV test. Women will be randomised to receive either a placebo or GBS6 vaccination after recruitment.

15.3. Participant confidentiality

All data will be handled in accordance with the Uganda Data Protection and Privacy Act 2019 and in accordance to the approved protocol, GCP, the UK Data Protection Act (1998), the St George's, University of London Information Governance Policy (or other local equivalent), the Research Governance Framework (2005 2nd edition) and the Sponsor's SOPs, as appropriate.

Participants will be allocated a unique identifier. Linkage to the participant will be broken at this point and the individual patients will no longer be identifiable to any of the study team. The exception will be if we identify a woman who has previously undiagnosed syphilis, hepatitis B or HIV infection at point of care screening. If this is the case, the woman will be informed and her results shared with the clinical team in order to provide the necessary health care and follow up required.

Guarantees of confidentiality and anonymity given to the research participants will be honoured, unless there are clear and overriding reasons (such as criminal offences) to do otherwise. Researchers will practice in accordance with the 'duty of confidentiality' and not pass on identifiable data to third parties without participants' consent.

Data will be stored on a validated online clinical trial database (REDCap). The data management department at MUJHU will provide guidance on the data quality control systems and tracking systems for patients and laboratory samples. (All lab samples will have a unique identifier). All aspects of the database will adhere to good clinical practice (GCP). Data and samples will be securely transferred between collaborators using only the unique study ID that will not be linked to patient identifiable information.

15.4. Participant information and consent

All data will be handled in accordance with the Uganda Data Protection and Privacy Act 2019 and in accordance to the approved protocol, GCP, the UK Data Protection Act (1998), the St George's, University of London Information Governance Policy (or other local equivalent), the Research Governance Framework (2005 2nd edition) and the Sponsor's SOPs, as appropriate

Participants will be allocated a unique identifier. Linkage to the participant will be broken at this point and the individual patients will no longer be identifiable to any of the study team. The exception will be if we identify a woman who has previously undiagnosed syphilis, hepatitis B or HIV infection at point of care screening. If this is the case, the woman will be informed and her results shared with the clinical team in order to provide the necessary health care and follow up required.

Guarantees of confidentiality and anonymity given to the research participants will be honoured, unless there are clear and overriding reasons (such as criminal offences) to do otherwise. Researchers will practice in accordance with the 'duty of confidentiality' and not pass on identifiable data to third parties without participants' consent.

Data will be stored on a validated online clinical trial database (REDCap). The data management department at MU-JHU will provide guidance on the data quality control systems and tracking systems for patients and laboratory samples. (All lab samples will have a unique identifier). All aspects of the database will adhere to good clinical practice (GCP). Data and samples will be securely transferred between collaborators using only the unique study ID that will not be linked to patient identifiable information.

15.5. Informed consent

This protool and the informed consents and any subsequent modifications will be reviewed and approved by the IRB responsible for oversight of the study. The consent form will describe the purpose of the study, the procedures to be followed, and the risks and benefits of participation. A copy of the consent form will be given to the participant.

If a potential participant is identified, the study team will go through the consent process with her, including review of the informed consent form (ICF) before enrolment. The consent and enrolment process will ensure with high confidence that potential participants understand the potential risks and benefit of the vaccine, the study procedures, their right to refuse and/or withdraw from the study at any point without affecting the health services or care they receive, and without having to disclose a reason for their refusal or withdrawal.

Participants will be required to read the full consent or have a full oral explanation in the presence of an impartial witness in an appropriate language before agreeing to be in the study. They will be given the opportunity to ask any questions and seek clarification. Written consent will then be obtained by a dated signature or thumbprint.

Participants who consent to be in the study will proceed through enrolment for vaccination and follow up.

15.6. Benefits to participants

The mothers and babies involved in the study will also have the benefit of meeting with and ask questions of experienced study team clinical staff for the duration of their enrolment. Morbidity will be closely monitored as a safety net for participants, and free access to basic health care will be provided to the mothers and their child. This includes basic medical treatment for non-severe infections (urinary, respiratory, malaria, skin infections etc.) provided at any of the study hospitals (open 24 hours). In most cases, if the family incurs costs at referring facilities or out of hours centres, these costs will be reimbursed by the study team. The free health care will be provided to our participants until the child is 12 months of age, (including participants subsequently excluded) as well as 24/7 access to study staff via mobile phones.

16. Data Management and sharing

16.1. Data collection tool

Data will be collected on tablets and input directly into RedCap by the clinical staff as each participant is recruited and at each follow up visit. For the laboratory data, data will be input into the database by the relevant laboratory technician as results become available.

16.2. Incidental findings

If a woman is found to be co-infected with syphilis, hepatitis B or C, or to have become infected with HIV at the screening visit, then she will be referred for ongoing care to the relevant clinical team. This will be made explicit in the patient information leaflet.

16.3. Data handling and analysis

Essential data for the study will be directly entered into the eCRF using the REDCap system, which will be stored on a secure SQL server at St George's University of London. If paper clinical record forms (CRFs) have to be used, they will be transcribed in to the RedCAP database as soon as possible. A database will be designed with the help of the MUJHU data manager. This will reflect the content of the study CRFs. All the scientific data will be maintained within a pre-designed database, which will be backed up on 2 external hard drives. The data management department at the MUJHU will provide guidance on the data quality control systems and tracking systems for patients and laboratory samples. The database will adhere to good clinical practice (GCP) where possible.

16.4. Data sharing

This work contributes to the advancement of scientific knowledge and the broadening of understanding of human physiology using state-of-the art laboratory methods. Our research aims to identify key antibody-mediated parameters as potential targets of future vaccine trials to prevent and treat infection in new-borns. A data sharing agreement will be arranged between collaborators.

16.5. Source documents and access to source data

The Principal Investigators will maintain appropriate medical and research records for this study in compliance with the principles of good clinical practice and regulatory and institutional, national and international regulatory requirements for the protection of confidentiality of participants. The study team members will have access to records. A photocopy of the maternity notes will be made at each visit with the hospital number obscured by a sticker prior to photocopying. These notes will be held securely in a locked cabinet on site in a locked office to which only the study co-ordinator or their delegate has the key. A photocopy of the hospital notes of any medical attendance will be arranged and stored in the same way as the maternity notes.

The authorised representatives of the sponsor and the ethics committee may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) for the participants in this study. The clinical study site will permit access to such records.

16.6. Archiving arrangements

The trial essential documents along with the trial database will be archived in accordance with the sponsor SOP JRESSOP0016. The agreed archiving period for this trial will be 15 years. This will include any study databases.

16.7. Direct access to source data

The Investigator(s)/institution(s) will permit trial-related monitoring, audits, REC review, and regulatory inspection(s), providing direct access to source data/documents. Monitoring, Inspections and record retention

16.8. Quality control/Quality assurance

Several steps will be undertaken to ensure the accuracy and reliability of the data collected while conducting this study and these will include selection of qualified study staff, review of the protocol and study procedures with all the study personnel before undertaking any study related activities as well as pre study and periodic monitoring visits. Guidelines for the completion of CRFs and handling of samples will be provided to study staff, and the accuracy and completeness of the study documents will be reviewed by a designated QC/QA personnel and the study monitor(s). Any discrepancies will be resolved by the responsible study staff or as appropriate. A specific monitoring plan will also be put in place before the start of the study.

16.9. Study monitoring

Monitors will participate in all key planned activities, collaborating with implementation of the study. They will therefore comply with all the planned monitoring visits.

The monitoring plan at the investigation site and frequency for the implementation of the monitoring visits is detailed in the study monitoring plan will be prepared prior to the study. The monitoring plan will cover instructions for monitoring the main aspects of the implementation of the clinical studies. Monitoring will be arranged by the Sponsors.

16.10. Study inspections

The investigators and institutions involved in the study will ensure that regulatory authorities may conduct monitoring and auditing and inspection of the study implementation. This includes official reviews of documents, facilities, records, and any other resources that are deemed by the authorities to be related to the study and that may be located at the study site or the Sponsor's facilities, or at other establishments deemed appropriate by the regulatory authority.

16.11. Audits

Audits can from time to time be instituted by the Sponsor and these will be undertaken in keeping with requirements of the protocol.

16.12. Source documents and access to source data

The Principal Investigators will maintain appropriate medical and research records for this study in compliance with the principles of good clinical practice and regulatory and institutional, national and international regulatory requirements for the protection of confidentiality of participants. The study team members will have access to records. A photocopy of the maternity notes will be made at each visit with the hospital number obscured by a sticker prior to photocopying. These notes will be held securely in a locked cabinet on site in a locked office to which only the study co-ordinator or their delegate has the key. A photocopy of the hospital notes of any medical attendance will be arranged and stored in the same way as the maternity notes.

The authorised representatives of the sponsor and the ethics committee may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) for the participants in this study. The clinical study site will permit access to such records.

16.13 Archiving arrangements

The trial essential documents along with the trial database will be archived in accordance with the sponsor SOP JREOSOP0016. The agreed archiving period for this trial will be 15 years. This will include any study databases.

17. Finance Medical care and Insurance

17.1. Finance

Funding from EDCTP (reference number: RIA2018V-2304)

17.2. Insurance and indemnity

Participants will be insured against any harm that results from their participation in this study. Professional indemnity will be provided, insurance cover will be obtained from a local insurance provider.

This insurance will be purchased from a Ugandan insurer in line with SOMREC recommendations.

18. Ethics and regulatory requirements

18.1. Ethical approval

It is the responsibility of the investigator to have prospective approval of the study protocol, protocol amendments, ICDs, and other relevant documents, e.g., recruitment advertisements, if applicable, from the IRB/EC. All correspondence with the IRB/EC should be retained in the investigator file. Copies of IRB/EC approvals should be forwarded to Pfizer.

The only circumstance in which an amendment may be initiated prior to IRB/EC approval is where the change is necessary to eliminate apparent immediate hazards to the participants. In that event, the investigator must notify the IRB/EC and Pfizer in writing immediately after the implementation.

The study will be conducted in accordance with the protocol, legal and regulatory requirements, and the general principles set forth in the International Ethical Guidelines for Biomedical Research Involving Human Participants (Council for International Organisations of Medical Sciences 2002), the ICH Guideline for Good Clinical Practice, and the Declaration of Helsinki.

18.2. Definition of the End of Trial

End of trial in all participating countries is defined as last participant last visit (LSLV). The REC requires notification of the end of trial within 90 days of its planned completion or within 15 days if the study is terminated early.

18.3. Annual Progress Reports (APRs)

The principal Investigator will prepare APRs in line with the stipulated ethical guidelines. The Principal Investigator will prepare the APR for all the relevant ethics and regulatory bodies in accordance with the stipulated guidelines. It will be reviewed by the MU-JHU compliance office and the study sponsor and sent to the main REC by the PI within 30 days of the

anniversary date on which the favourable opinion was given by the Ethics committee, and annually until the trial is declared ended.

18.4. Publication policy

The results of this study will be important to share with the medical community. Any proposed publication or other type of disclosure of the results of the study (collectively, "publication") that result from this work will follow ICHMJE guidelines with the agreement on contributing authors, and outlines prior to the initiation of writing the publication. Once all authors have finalized the disclosure, to ensure against inadvertent disclosure of confidential information or unprotected inventions, the publication will undergo review at the participating institutions (including Pfizer) before it is submitted or otherwise disclosed.

If any patent action is required to protect intellectual property rights, the investigator agrees to delay the disclosure for a period not to exceed an additional 60 days.

The investigator will, on request, remove any previously undisclosed confidential information before disclosure, except for any study- or Pfizer product-related information necessary to the appropriate scientific presentation or understanding of the study results.

If the study is part of a multicenter study, the investigators agree that the first publication is to be a joint publication covering all investigator sites, and that any subsequent publications will reference that primary publication.

For all publications relating to the study, the institution will comply with recognised ethical standards concerning publications and authorship, including Section II - "Ethical Considerations in the Conduct and Reporting of Research" of the Uniform Requirements for Manuscripts Submitted to Biomedical Journals, http://www.icmje.org/index.html#authorship, established by the International Committee of Medical Journal Editors.

18.5. Before the official completion of the Trial

All publications during this period are participant to permission by the Sponsor. If an investigator wishes to publish a sub-set of data without permission by the Sponsor during this period, the Trial Management Group shall have the final say.

Exempt from this requirement are student theses that can be submitted for confidential evaluation but are participant to embargo for a period not shorter than the anticipated remaining duration of the trial.

18.6. Up to 180 days after the official completion of the Trial

During this period the Principal Investigator shall liaise with all investigators and strive to consolidate data and results and submit a manuscript for peer-review with a view to publication in a reputable academic journal or similar outlet as the Main Publication.

- The Chief Investigator shall be senior and corresponding author of the Main Publication.
- Insofar as compatible with the policies of the publication outlet and good academic practice, the other Investigators shall be listed in alphabetic order.
- Providers of analytical or technical services shall be acknowledged, but will only be listed as authors if their services were provided in a non-routine manner as part of a scientific collaboration.
- Members of the Trial Management Group shall only be acknowledged as co-authors as per ICIME guidelines.
- If there are disagreements about the substance, content, style, conclusions, or author list of the Main Publication, the Principal Investigator shall ask the Trial Management Group to arbitrate.

18.7. Beyond 180 days after the official completion of the Trial

After the Main Publication or after 180 days from Trial end date any Investigator or group of investigators may prepare further publications. In order to ensure that the Sponsor will be able to make comments and suggestions where pertinent, material for public dissemination will be submitted to the Sponsor for review at least sixty (60) days prior to submission for publication, public dissemination, or review by a publication committee. Conference posters should be submitted at least (14) days prior to presentation. Sponsor's reasonable comments shall be reflected. All publications related to the Trial shall credit the Principal and Co-Investigators as co-authors where this would be in accordance with normal academic practice and shall acknowledge the Sponsor and the Funders.

19. SIGNIFICANCE AND BENEFICIARIES OF THE PROPOSED WORK

To our knowledge, this will be the first well-powered intervention study to investigate the immunogenicity of a hexavalent GBS vaccine which will facilitate the development of a safe and effective GBS vaccine.

The beneficiaries of this research will be:

- Academics
- Research participants, their schools and communities
- Public health policy makers
- Populations of low- and middle-income countries
- Populations of high-income countries

ACADEMICS, including immunologists, vaccinologists and epidemiologists will obtain immediate benefit from the results which will answer current questions on the drivers and mediators of population differences in vaccine responses. The results will provide evidence to guide vaccine development (in the medium term; with commercial implications in the longer term) and inform strategies for future testing of vaccines in LMICs. As well, an important archive will be developed providing opportunities for additional studies.

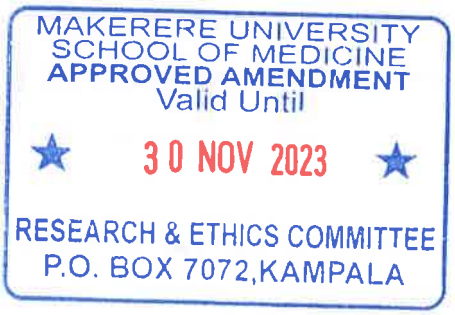
RESEARCH PARTICIPANTS will obtain immediate and lasting benefit from the provision of relevant immunisations only some of which are currently freely available through the Ministry of Health. As well, they will receive education about infection and vaccines resulting in improved health awareness for individuals, families and communities.

PUBLIC HEALTH POLICY MAKERS, including the Ugandan Ministry of Health and Ministry of Education and internationally WHO, will obtain immediate benefit from results regarding the impact of HIV infection on maternal vaccine responses and the degree to which effects

are reversed by intensive intervention in the short term. This will help to inform policy regarding the introduction and monitoring of maternal vaccines in Uganda.

Our ultimate goal is that POPULATIONS OF LOW- AND MIDDLE-INCOME COUNTRIES will benefit from this vaccine (perhaps tailor-made for the environment), resulting in a reduced burden of infectious diseases, enhanced human capital and improved economic development. An area of particular benefit may be the development of effective vaccines for endemic infections such as HIV, tuberculosis and malaria. For these infections, vaccine development so far has been challenging and vaccine responses impaired, or vaccine efficacy modest in tropical LICs. Effective new vaccines are also needed in LICs for emerging and re-emerging viral infections, such as Ebola and Zika, and for infections (such as bacterial causes of gastroenteritis) which are prone to the development of drug resistance.

POPULATIONS OF HIGH-INCOME COUNTRIES will also, in the long-term, benefit from improved vaccines, as well as from a reduced risk from endemic, emerging and re-emerging infectious diseases with reservoirs in low- and middle-income countries.



20. PLANS FOR COMMUNICATION AND DISSEMINATION

This research is relevant to those seeking a basic understanding of how HIV infection impacts immune responses to vaccination in pregnancy in humans; seeking to develop vaccines with ideal characteristics for tropical LICs; and implementing public health programmes for immunisation.

COMMUNICATION WITH ACADEMICS. Within our institutions (SGUL and MJUHU) we will participate in relevant cross-cutting Centres, in theme meetings, science meetings, seminars and news bulletins, to promote opportunities for internal collaboration.

To communicate with other academics, we will employ publications, conferences, collaborative networks and websites. Besides our institutional websites we have established a specific website for our study which will highlight the proposed work on vaccines.

www.sgul.ac.uk

www.gbsatgeorges.ac.uk

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PUBLIC HEALTH POLICY MAKERS. Our collaborators Dr Mwanga (Director of Epicentre, Uganda) and Dr Luzze (Uganda National Expanded Programme on Immunisation) will be members of our steering group, participating in all aspects of the programme and advising on dissemination. As well, we will participate in meetings with policy makers at both district and national level. We will provide simple practical results digests and briefs for policy-makers, highlighting the extent to which our findings have direct policy implications. We also link to in-country officers of the World Health Organisation (WHO). We will correspond directly with WHO head office, when appropriate.

RESEARCH PARTICIPANTS and COMMUNITIES. We will hold meetings with research participants and community leaders both before the start of the work, and to share the results. We will work with community advisory boards to aid public engagement activities.

WIDER PUBLIC IN UGANDA. A key approach to communication with the wider public in Uganda will be Open Days for schools and undergraduates. These were initiated in 2009 at the Uganda Virus Research Institute by our capacity development programme, the Makerere University UVRI Centre of Excellence for Infection & Immunity Research and Training (MUII). Each has hosted about 2000 participants. Open Day planning includes consultative meetings with teachers to ensure relevance to students' needs. Open Days facilitate intense engagement with the press. As well, we will exploit other opportunities for engagement with the public and local media.

www.muii.org.ug

WIDER GLOBAL PUBLIC. We will engage with the global public through our websites (see above) and through the international media, working with our Communications teams to ensure regional and international (as well as local) coverage of significant results.

21. Statement of compliance

The trial will be conducted in compliance with the protocol, Sponsor's Standard Operating Procedures (SOPs), GCP and the applicable regulatory requirement(s).

The study conduct shall comply with all relevant laws of Uganda and the Human Rights Act 1998, the Data Protection Act 1998, the Human Medicines Regulations 2012, ICH GCP, the World Medical Association Declaration of Helsinki entitled 'Ethical Principles for Medical Research Involving Human Participants' (2008 Version), the NHS Research Governance Framework for Health and Social Care (Version 2, April 2005).

This study will be conducted in compliance with the protocol approved by the REC and according to GCP standards. No deviation from the protocol will be implemented without the prior review and approval of the Sponsor and REC except where it may be necessary to eliminate an immediate hazard to a research participant. In such case, the deviation will be reported to the Sponsor and REC as soon as possible.

22. List of Protocol appendices

23. References

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