The immunogenicity of Shingrix vaccination in people living with HIV at risk of shingles infection (SAGE)

Protocol Short Title/ Acronym: SAGE

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Trial Identifiers

IRAS Number:	1004647
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1. Study Synopsis

Title of clinical trial	The immunogenicity of Shingrix vaccination in people living with HIV at risk of shingles infection (SAGE)
Protocol Short Title	SAGE
Trial Phase	Phase 4 (post marketing study)
Sponsor name	Guys and St Thomas' NHS Foundation Trust
Chief Investigator	Dr Julie Fox
IRAS number	1004647
Medical condition under investigation	Herpes zoster
Purpose of clinical trial	To determine if the Shingrix vaccine is immunogenic for people living with HIV who are ≥ 50 years of age OR have perinatally acquired HIV infection and are aged 18 and over.
Primary objective	To assess the cell-mediated and humoral immunity profile of the Shingrix vaccine in HIV positive adults aged 50 years and over, and those with perinatally acquired HIV infection and are aged 18 and over.
Secondary objectives	1. Detailed characterization of cell-mediated and humoral responses to the candidate vaccine 2. To assess the impact of current CD4, nadir CD4, CD4: CD8 on immunogenicity 3. To assess the impact of vaccination on HIV reservoirs 4. To explore BCR and TCR repertoires in response to vaccination. 5. To investigate the sequences of viruses from individuals who develop shingles after vaccination.

	6. To assess the safety of the Shingrix vaccine in HIV positive adults aged 50 years and over, and those with perinatally acquired HIV infection aged 18 and over.
Trial design	Open, single arm intervention study
Endpoints	**Primary endpoints** 1. Total VZV specific cell mediated geometric mean titer (GMT) ratios change from baseline to week 12 (4 weeks after second vaccine dose) 2.Total VZV specific antibody geometric mean titer (GMT) ratios change from baseline to week 12 (4 weeks after second vaccine dose) **Secondary endpoints** 1. Change of VZV specific cell mediated mediated geometric mean titer (GMT) ratios change from baseline to week 48 2. Change of VZV specific antibody mediated geometric mean titer (GMT) ratios change from baseline to week 48 3. Occurrence of adverse events of Grade 3 or higher severity 4. Viral sequence of shingles infections
Sample size	70 (61 evaluable)
Summary of main eligibility criteria *(see sections 5.1/5.2 of protocol for fully eligibility criteria)*	Inclusion criteria: 1. HIV positive ≥50 years **OR** 2. Perinatally acquired HIV-positive individuals who are aged 18 and over. Exclusion criteria: 1. Received shingles vaccine in past 12 months

	2. Active herpes zoster disease in past 6 months preceding the first dose of study vaccine 3. Pregnant or unwilling to use contraception
IMP, dosage and route of administration	Vaccination schedule: week 0, week 8
Active comparator product	nil
Maximum duration of treatment of a participant	2 months
Version and date of protocol amendments	

2. Glossary of Terms

AE	Adverse Event
AR	Adverse Reaction
BCR	B cell receptor
CA	Competent Authority
CI	Chief Investigator
CRF	Case Report Form
CRO	Contract Research Organisation
CTA	Clinical Trial Authorisation
CTIMP	Clinical Trial of Investigational Medicinal Product
CTU	Clinical Trials Unit
DMC	Data Monitoring Committee
DSUR	Development Safety Update Report
EC	European Commission
EMEA	European Medicines Agency
EU	European Union
EUCTD	European Clinical Trials Directive
EudraCT	European Clinical Trials Database
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
IB	Investigator Brochure
ICF	Informed Consent Form
IMP	Investigational Medicinal Product
IMPD	Investigational Medicinal Product Dossier
ISF	Investigator Site File (This forms part of the TMF)
ISRCTN	International Standard Randomised Controlled Trials Number
MA	Marketing Authorisation
MHRA	Medicines and Healthcare products Regulatory Agency
PI	Principal Investigator
PIS	Participant Information Sheet
QA	Quality Assurance
QC	Quality Control
QP	Qualified Person
REC	Research Ethics Committee
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SDV	Source Data Verification
SOP	Standard Operating Procedure
SmPC	Summary of Product Characteristics
SUSAR	Suspected Unexpected Serious Adverse Reaction
TCR	T cell receptor
TMF	Trial Master File
TMG	Trial Management Group
TSC	Trial Steering Committee
VZV	Varicella-zoster Virus

Table of Contents

3. Background & Rationale

Varicella-zoster Virus (VZV) causes two distinct diseases. Varicella (chickenpox) shortly occurs after primary VZV infection and is characterised by systemic illness and a widely disseminated rash. Herpes zoster (shingles) occurs when VZV reactivates from latency and typically manifests as a localised, dermatomal rash. The typical herpes zoster (HZ) rash usually lasts 2 to 4 weeks and is usually accompanied by pain that is often described as burning, shooting, or stabbing. In some people, even touching the affected area lightly may cause pain, a phenomenon known as allodynia. This HZ-associated pain may be severe, and pruritus, which can also be severe, may be as common as pain.

The most common complication of HZ is postherpetic neuralgia (PHN). PHN is defined as pain that persists after the resolution of the HZ rash. Affected patients typically report constant burning, throbbing, intermittent sharp or electric shock-like pain, or allodynia. Older age is a clear risk factor for PHN. Other risk factors may include a severe HZ rash and a painful HZ prodrome. PHN tends to improve over a period of months. About 70- 80% of cases resolve within 1 year, however, in some persons PHN persists for many years [Dworkin, 2007].

Age is the most common risk factor for developing HZ. The incidence of HZ is relatively constant at 2-3 cases per 1000 persons per year until age 40, and then increases progressively with age: At 50-59 years of age (YOA) the incidence is about 5 cases per 1000 persons per year, and it increases to 10 cases per 1000 persons per year in people ≥ 60 YOA [CDC, 2008; Oxman, 2005].

While most HZ incidence data come from the United States (US) and Europe, available data indicate similar incidences of HZ in other parts of the world including Japan, Korea, Australia and Latin America [Araújo, 2007; Garcia Cenoz, 2008; Kang, 2008; Toyama, 2009]. Half of all HZ cases occur in patients over the age of 60, and individuals who reach 85 years old have a 50% chance of having HZ during their lifetime [Oxman, 2005]. The risk for PHN is also highest in older people with HZ, occurring in 18-50% of those aged 70 years and older [Oxman, 2005; Scott, 2006].

People with impaired cell-mediated immunity (CMI) due to disease, drug treatment, medical interventions or advanced age are at increased risk for the development of HZ [Cohen, 2007]. Since the loss of VZV specific T cell responses as a result of aging or immunosuppression leads to heightened susceptibility to HZ, vaccination is considered a means to reduce the risk of HZ in older adults and immunocompromised persons [Oxman, 2005; Sperber, 1992].

Shingles in people living with HIV

People living with HIV have a higher risk of developing HZ. This risk is attenuated but does not return to age-matched population rates after commencement of anti-retroviral therapy (ART) and remains approximately 3–5 times higher (Moanna 2013). Shingles may occur and may recur at any time during HIV infection, although a low CD4 cell count and a viral load >400 copies/mL have been associated with a higher risk [Blank 2012: Glesby 1995: Shearer 2014]. Additional risk factors may include a prior episode of shingles, crack cocaine use, and age >60 years (>40 years in crack cocaine users) [Nacher 2013: Shearer 2014].

Complications of shingles are also more common in HIV-positive subjects than in the age-matched general population (27–28% vs. 10–13%) [Blank 2012:Glesby 1995], and may include cutaneous dissemination, chronic atypical skin lesions, ocular and neurological complications, or visceral dissemination. Acute retinal necrosis and neurological syndromes can occur as a result of VZV reactivation in the absence of rash. Both shingles and VZV-mediated cerebral vasculitis causing stroke have also been recognised as a manifestation of the immune reconstitution inflammatory syndrome [Tangsinmankong 2004, Teo 2014].

People living with HIV may have less functional immunity and have more associated co-morbidities than the general population. Consistent with data from other vaccines [Grilli 2014: Maves 2014], it is highly possible that they may, therefore, have a less robust response to herpes zoster vaccination and that this may be more pronounced with increased age.

Correlates of protection

Although no immunological correlate for protection against HZ has been identified, current knowledge suggests that VZV-specific CMI is of primary importance in preventing HZ [CDC, 2008]. The role of humoral immune responses in preventing HZ is less clear. However, VZV-specific antibodies (Abs) may help control viral dissemination in immunocompromised persons and may thereby help limiting the severity of HZ. Furthermore, a correlation between post-vaccination anti-VZV Ab concentrations and protection against HZ was observed in the Zostavax efficacy study [Levin, 2008]. While VZV-specific Abs may not be directly protective against HZ, they may represent a “downstream” measure of the CMI response to vaccination.

Shingles vaccine in the UK

The available shingles vaccine (Zostavax) contains high dose, replicating live attenuated VZV (Oka/Merck strain). The shingles vaccine is at least 14 times more potent than the chickenpox vaccine [Harpaz 2008]. It is given as a single dose by subcutaneous injection and is licensed for adults aged ≥50 years [NHS 2021]. Vaccination of immunocompetent adults aged ≥60 years boosts natural immunity and reduces the incidence of shingles by half and the incidence of PHN by two-thirds [Oxman 2005]. The vaccine is also efficacious in immunocompetent adults aged 50–59 years, and protection against shingles lasts for at least 5 years [Schmader 2012: Schmader 2012: Gagliardi 2012]. A systematic review concluded that there is a clear benefit in vaccinating elderly patients, with no major safety concerns [Gagliardi 2012]. The inactivated subunit vaccines based on the VZV glycoprotein E (gE) antigen, such as SHINGRIX, are efficacious [Levin, 2008] [Berkowitz 2015] and soon to be available in the UK.

Indications for Shingles vaccine in the UK

In the UK, shingles vaccination (Zostavax) is recommended for adults without a history of immunodeficiency aged 70 years, and a ‘catch- up’ programme currently

targets those aged 70–79 years. Contraindications include pregnancy and breast feeding and significant immunocompromise [BHIVA 2015].

For individuals living with HIV, British HIV association (BHIVA) vaccine guidelines 2015 November recommend that patients ≥60 years of age (provided the CD4 cell count is >200 cells/μL) should receive the shingles vaccine (Zostavax) vaccine [Aberg 2014], which is 10 years younger than national recommendations. There are safety and efficacy concern however, giving this live vaccine to "special populations" such as those with a low nadir CD4 [Benson 2012] or those with perinatal infection in which shingles vaccines have not been evaluated at all.

Thanks to the continuously increasing coverage of ART-based prophylaxis and treatment, in 2018, MTCT incidence was under 2%, and about 50% of children living with HIV were receiving ART [UNAIDS 2019]. Therefore, an increasing number of children start ART at a very young age and will be receiving antiretroviral drugs for all their lifetime. ART greatly improved their survival and the quality of life [Gibb 2003: Judd 2007], but on the other hand, they now face the consequences of a lifelong chronic condition, suffering from pathogenic mechanisms typical of premature aging [Deeks 2009: Brady 2010: Chiappini, 2014: Guaraldi 2017]; i.e., they show an increased risk of age-associated comorbidities, identified as non-AIDS-related diseases [Klein 2011: Brouilette, 2007: Takata 2012], compared to healthy individuals [Deeks 2012: Guaraldi, 2011: Smith 2013]. Those with perinatal infection have poor immune function for a variety of reasons: such early HIV infection impacts T-Cell memory (McCarty 2018), poor access to ART during childhood (UNAIDS 2019), partly as paediatric formulations were not readily available until 2000, and finally their adherence to ART is often variable during early and teenage years for sociological reasons [MacDonell 2016: Gray 2017: Schlatter 2016]. Such young individuals, who are at risk of Shingles, historically find it difficult to attend for regular follow up. Therefore to mimic real life, this study has included large window periods. This will not impact vaccine efficacy, which allows up to 6 months between vaccination (Santos Virology 2000: Tipples Emerg Inf Dis 2002). furthermore, if vaccinations are being given earlier than previously recommended then knowledge of the duration of protection is imperative to be able to inform on recommendations for booster vaccination.

Shingrix vaccine

HZ/Su (SHINGRIX) is the first subunit vaccine developed to protect against shingles and is licensed for use in the USA [CDC 2020] and the EU [EMA 2021], among other regions. The efficacy against HZ and immune responses to RZV is durable and suggests that the clinical benefit of RZV in older adults is sustained for at least 7 years post-vaccination (Boutry 2021).

The dosing guidance as Per the SmPC is as follows:

The primary vaccination schedule consists of two doses of 0.5 mL each: an initial dose followed by a second dose 2 months later. If flexibility in the vaccination schedule is necessary, the second dose can be administered between 2 and 6

months after the first dose. For subjects who are or might become immunodeficient or immunosuppressed due to disease or therapy, and whom would benefit from a shorter vaccination schedule, the second dose can be given 1 to 2 months after the initial dose.

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Shingles vaccine in pregnancy

Shringrix is not licenced for use in pregnancy as there is no data on SHINGRIX in pregnancy from clinical trials. As pregnancy itself is a risk factor for shingles (Buvelot 2016) there is a need to include women of childbearing age into vaccine studies. Studies including women, without the need for double contraception, are urgently needed to reduce stigma around vaccination during pregnancy.

Shingles breakthrough infection

Viruses that contain mutations in gE epitopes have been described in the immunocompromised (Zweygberg Wirgart 2006: Schmidt-Chanasit 2007). sequencing would exclude the likelihood that these are overrepresented in cases of post vaccination shingles in this population. Immunosuppressed individuals are also more likely to reactivate multiple VZV strains and this in turn may be associated with more severe disease (Depledge JID 2018) These can be identified using haplotype reconstruction methods that we have developed for DNA viruses eg HaROLD (Pang 2020).

Shingrix vaccine in HIV

Data in all age groups and in people living with HIV for the SHINGRIX vaccine is limited. From July 2021, the vaccine has approval for use in immunocompromised people aged 18 and over and this includes individuals living with HIV.

The safety and immunogenicity of the HZ/Su vaccine (SHINGRIX) in HIV was supported through a small randomized placebo-controlled study [Berkowitz 2015], however this study did not evaluate the impact of age, nadir CD4 or mode of HIV transmission. Furthermore, the few numbers of patients in the low CD4 group completing the study meant analysis was not possible. No investigation of shingles vaccines in those born with HIV has ever been carried out, despite these individuals suffering from shingles at a much younger age than those acquiring HIV later in life (Fidler personal communication). This important subgroup is excluded from vaccination due to the age threshold for vaccination [BHIVA guidelines 2015: CDC 2020]. Evaluating outcomes to the Shingrix vaccine allows us to compare responses across age groups, helping to inform global policy on Shingles vaccine implementation in areas of high HIV prevalence. If we are to vaccinate people younger, then the durability of the immune response is important to understand boosting timelines.

In this initial study, we will explore cellular and humoral immune responses generated amongst PLWH on ART who are 50 years old and over OR have perinatally acquired HIV infection stratified by nadir CD4 count. The results will generate new European data and will be used to facilitate guidelines changes and allow its usage in individuals living with HIV. This represents the first investigation of shingles vaccination in individuals with who were born with HIV. If we obtain further

funds, we will extend the study to 2 years to evaluate durability of immune response to vaccination.

4. Trial Objectives and Design

4.1. Trial Objectives

Overall research question: Is the Shingrix vaccine immunogenic in people living with HIV who are either 50 years of age and over, or over OR have had HIV from birth.

Primary objective: To assess the cell-mediated and humoral immunity profile of the Shingrix vaccine in adults living with HIV aged 50 years and over, and in those with who have had HIV from birth, who are aged 18 and over.

Secondary objectives:

1. Detailed characterization of cell-mediated and humoral responses to the candidate vaccine
2. Impact of current CD4, nadir CD4, CD4: CD8 on immunogenicity.
3. Impact of vaccination on HIV reservoirs.
4. To explore BCR and TCR repertoires in response to vaccination.
5. To investigate the sequences of viruses from individuals who develop shingles after vaccination.
6. To assess the safety of the Shingrix vaccine in people living with HIV aged 50 years and over, and those born with HIV, who are 18 years and over.

4.2. Primary endpoints

1. Total VZV specific cell mediated geometric mean titer (GMT) ratios change from baseline to week 12 (4 weeks after second vaccine dose).

2.Total VZV specific antibody geometric mean titer (GMT) ratios change from baseline to week 12 (4 weeks after second vaccine dose).

4.3. Secondary endpoints

1. Change of VZV specific cell mediated mediated geometric mean titer (GMT) ratios change from baseline to week 48
2. Change of VZV specific antibody mediated geometric mean titer (GMT) ratios change from baseline to week 48
3. Occurrence of adverse events of Grade 3 or higher severity
4. Viral sequence of shingles infections

4.4 Exploratory endpoints

1. Antigen-specific antibody (Ab) concentrations mediated geometric mean titer (GMT) ratios change from baseline to week 12 (4 weeks after second vaccine dose)in subjects with suspected and confirmed HZ
2. Antigen-specific antibody (Ab) concentrations mediated geometric mean titer (GMT) ratios change from baseline to week 12 (4 weeks after second vaccine dose)in subjects with suspected and confirmed HZ
3. HIV reservoirs will be correlated with Antigen-specific antibody (Ab) concentrations
4. BCR and TCR repertoires will be correlated with Antigen-specific antibody (Ab) concentrations

4.5. Trial Design

An open label, single arm, intervention study. This prospective multicentre study will recruit 70 individuals attending outpatient HIV services. Individuals will attend for visits at screening, baseline (first vaccine dose), week 4, week 8 (second vaccine dose), week 12, week 24 and week 48. Research and safety blood samples will be taken at each visit. Study participants will receive 2 intramuscular doses of HZ/su 2 months apart. For any individual who develops shingles after vaccination will have swabs taken for viral diagnosis and viral sequencing; these individuals will also have a blood sample taken. Tolerability of vaccination, including local and systemic adverse events will be recorded.

4.6. Trial Assessment Schedule for Investigators (Table 1)

Visit number	1	2	3	4	5	6	7
	Screening*	Baseline					
Week number (window period)		0 (+ 8 weeks)	4 (+/-3 weeks)	8 (+/- 3 weeks weeks)	12 (+/-3 weeks)	24 (+/-3 weeks)	48 (+/-3 weeks)
Written informed consent	X						
Eligibility assessment	X	X					
Demographics	X						
Medical History	X						
Vital Signs	X	X	X	X			
Temperature	X	X		X			
Full Physical Exam	X						
Directed Physical Exam		X	X	X	X	X	X
Concomitant medications	X	X	X	X	X	X	X
Adverse events unsolicited AEs and SAEs and IMD review	X	X	X	X	X	X	X
Vaccination		X		X			
Solicited general Adverse Events (Table 3)			X		X		
Survey		X					
Urine pregnancy test**	X	X		X			
CD4 (CD4:CD8)		X					X
HIV viral load		X				X	X
Hepatitis BsAg		X					
Safety blood samples FBC, U&E, ALT		X				X	X
Blood samples for Immunology analysis		X	X	X	X	X	X
Blood samples for Serology analysis		X	X	X	X	X	X

*screening and baseline can occur on the same day

**Pregnancy test must be performed even if the subject is menstruating at the time of the study visit.

Table 2: Procedures to be performed for each suspected HZ case

Clinical history
Perform clinical examination
Collect samples from all sites with clinical suspicion of HZ (eg skin, CSF, vitreous fluid). The following samples should be taken from each site (there may be more than one site per person presentation. - *1 swab to local lab for VZV PCR* - *1 swab to GOSH/University College London*
Record relevant clinical information regarding HZ in eCRF by study staff/investigator including - Date of onset of symptoms - Location of symptoms - Severity of symptoms - Signs
Blood sample: ACD and SST tubes to be sent to Imperial College London laboratory (From Guys and St Thomas' NHS Foundation Trust or Imperial College NHS Healthcare Trust) or University of Oxford (from Oxford University Hospitals NHS Foundation Trust)

5. Trial Medication

5.1. Investigational Medicinal Product

Shingrix powder and suspension for suspension for injection.

To be supplied by GSK as commercial stock to Sponsor site.

One pack of Shingrix consists of:
• Powder (antigen) for 1 dose in a vial
• Suspension (adjuvant) for 1 dose in a vial

The powder is white.

The suspension is an opalescent, colourless to pale brownish liquid.

Storage requirements: between 2º and 8ºC (36º and 46ºF). Protect from light.

As this is a low risk Type A trial, with no higher risk to the participant than standard of care and the trial will use commercially available IMP in accordance with the SmPC, no labelling in addition to standard dispensing labelling is required. However, study medication will be dispensed by the site's pharmacy against a trial specific prescription.

5.2. Dosing Regimen

Intra-muscular injection into the non-dominant arm at Week 0 and Week 8..

No special dietary or “life-style” requirements will be imposed.

5.3. IMP Risks

The Reference Document is the Summary of Product Characteristics (SmPC). The latest SmPC published for the UK is https://www.medicines.org.uk/emc/product/12054/smpc#gref.

The vaccine is administered intramuscularly.

Syncope (fainting) can occur following, or even before, any vaccination as a psychogenic response to the needle injection.

In adults aged ≥ 50 years, the most frequently reported adverse reactions were pain at the injection site (68.1% overall/dose; 3.8% severe/dose), myalgia (32.9% overall/dose; 2.9% severe/dose), fatigue (32.2% overall/dose; 3.0% severe/dose) and headache (26.3% overall/dose; 1.9% severe/dose). Most of these reactions were not long-lasting (median duration of 2 to 3 days). Reactions reported as severe lasted 1 to 2 days.

In adults ≥ 18 years of age who are immunodeficient or immunosuppressed due to disease or therapy (referred to as immunocompromised (IC)), the safety profile was

consistent with that observed in adults 50 years and over. There are limited data in adults aged 18-49 years at increased risk of HZ who are not IC.

Female participants of childbearing potential have to practice adequate contraception from 30 days before vaccination until 2 months after dose two and had to have a negative pregnancy test on the days of both vaccinations, prior to injection.

5.4. Drug Accountability

The pharmacy clinical trials team must maintain accurate accountability records of the IMP, including, but not limited to, the number of vaccines received, the number of vaccines dispensed to which subject, batch number, expiry date, and date of transaction in addition to the quantity of investigational product returned by the subject. Whilst it is acceptable to use standard hospital stock where necessary, some (commercial supply) IMP will be provided for trial use from GSK. The sponsor will determine the monitoring of accountability as per the risk assessment.

Any unused IMP and/or empty packaging will be returned to pharmacy for accountability. Destruction of IMP must be in accordance with the site IMP destruction SOP.

Following IMP destruction, the pharmacist at each site must complete a disposal/destruction log and file in the site file.

5.5. Storage and handling of study vaccine

All study vaccines to be administered to the subjects must be stored in a safe and locked place with no access by unauthorised personnel. The study vaccines will be stored at the defined temperature range (i.e. +2 to +8°C/36°F to 46°F) and must not be frozen. The storage temperature of the vaccine will be monitored daily with validated temperature monitoring device(s). The storage conditions will be assessed during pre-study activities under the responsibility of the sponsor study contact. Any temperature deviation, i.e. temperature outside the defined range (+2 to +8°C/36°F to 46°F of storage), must be reported to the sponsor as soon as detected. Following an exposure to a temperature deviation, vaccines will not be used until written approval has been given by the Sponsor.

Sponsor clinical trial pharmacy will be responsible for the temperature controlled transfer of trial medication to participating sites using an appropriate courier. This will be guided by a Trial Specific Procedure (TSP) drafted by the Sponsor Clinical Trials Pharmacy.

5.5.1. Dosage Preparation and administration of study vaccine

The powder and suspension should be inspected visually for any foreign particulate matter and/or variation of appearance. If either is observed, do not reconstitute the vaccine.

How to prepare Shingrix:

Shingrix must be reconstituted prior to administration.

1. Withdraw the entire contents of the vial containing the suspension into the syringe.

2. Add the entire contents of the syringe into the vial containing the powder.

3. Shake gently until the powder is completely dissolved.

The reconstituted vaccine is an opalescent, colourless to pale brownish liquid.

The reconstituted vaccine should be inspected visually for any foreign particulate matter and/or variation of appearance. If either is observed, do not administer the vaccine.

After reconstitution, the vaccine should be used promptly; if this is not possible, the vaccine should be stored in a refrigerator (2°C – 8°C). If not used within 6 hours it should be discarded.

Before administration:

1. Withdraw the entire contents of the vial containing the reconstituted vaccine into the syringe.

2. Change the needle so that you are using a new needle to administer the vaccine.

Any solution in excess of 0.5mL should be expelled. After confirming that the needle is not in a blood vessel, the reconstituted vaccine should be administered by IM injection, preferably into the deltoid muscle of the non-dominant upper arm, using a standard aseptic technique. The injection site should be on the same arm for all injections for an individual subject. In rare situations when there is no other alternative, the second injection may be given on the different arm.

Contraindications to subsequent vaccination

The following events constitute absolute contraindications to further administration of the vaccine. If any of these events occur during the study, the subject must not receive additional doses of vaccine but may continue other study procedures at the discretion of the investigator.

- Anaphylaxis following the administration of vaccine(s);
- Acute disease and/or fever at the time of vaccination. – Fever is defined as temperature ≥ 37.5°C (99.5°F) on oral, axillary or tympanic setting. The preferred route for recording temperature in this study will be oral. Subjects with a minor illness (such as mild diarrhoea, mild upper respiratory infection) without fever can be administered all vaccines.

5.6. Concomitant Medication

At each study visit/contact, the investigator should question the subject about any medication taken and vaccination received by the subject. Concomitant medication must be recorded in the log.

For management of concomitant therapies, please refer to the SmPC. A complete listing of all concomitant medication received during the treatment phase must be recorded in the relevant CRF.

6. Selection and Withdrawal of Participants

6.1. Inclusion Criteria

1. Able and willing to comply with the requirements of the protocol.
2. Able and willing to provide fully informed consent.
3. Male or non-pregnant, non-lactating females.
4. People living with HIV ≥50 years **OR** have perinatally acquired HIV and are aged 18 and over.
5. If female, of child-bearing age, not sterilised and participating in sexual intercourse that could result in pregnancy, using at least 1 acceptable method of contraception when engaging in sexual activities that can result in pregnancy, beginning at screening through month 4. Acceptable methods of contraception include the following:
    - Hormonal contraception.
    - Male or female condom.
    - Diaphragm or cervical cap with a spermicide.
    - Intrauterine device.

6.2. Exclusion Criteria

1. Active herpes zoster disease in past 6 months preceding the first dose of study vaccine
2. If female, planning to get pregnant, currently pregnant (evidence from positive serum or urine pregnancy test), or breastfeeding.
3. Used any investigational or non-registered product other than the study vaccine within 30 days preceding the first dose of study vaccine or planned use during the study period.
4. Vaccinated within the 12 months preceding the first dose of study vaccine or planned to be vaccinated during the study with a (non-study) vaccine against herpes zoster or varicella zoster virus.
5. History of any reaction or hypersensitivity likely to be exacerbated by any vaccine component.
6. Received or planned to receive a live vaccine in the period starting 30 days before the first dose of study vaccine and ending 30 days after the last dose

of study vaccine or had received or planned to receive a non-replicating vaccine within 8 days before or within 14 days after either dose of study vaccine.

7. Acute disease and/or fever at the time of enrolment; – Fever is defined as temperature ≥ 37.5°C (99.5°F) on oral, axillary or tympanic setting. The preferred route for recording temperature in this study will be oral. – Subjects with a minor illness (such as mild diarrhoea, mild upper respiratory infection) without fever may, be enrolled at the discretion of the investigator.

8. Chronic administration (defined as more than 15 consecutive days) of immunosuppressants or other immune-modifying drugs within six months prior to the first vaccine dose. For corticosteroids, this will mean prednisone < 20 mg/day, or equivalent, is allowed. Inhaled and topical steroids are allowed.

   Drugs include: Chemotherapeutic drugs, Immunomodulators and systemic immunosuppressive treatments, Oral glucocorticoids >20 mg/day, Cyclosporine, Methotrexate, Interleukins and/or cytokines, Immunotherapies (including TNF blockers).

9. Any other clinical condition that, in the opinion of the investigator, might pose additional risk to the subject due to participation in the study.

10. History of potential immune-mediated disease (pIMD). Note: If the subject has any condition on the list of pIMDs specified in the protocol, they must be excluded unless the aetiology is clearly documented to be non-immune mediated.

6.3. Selection of Participants

Participants will be recruited from HIV clinical centres which jointly provide medical care for over 10,000 PLWH: and combined have one of the largest European cohort of individuals with perinatally acquired HIV infection.

We will recruit up to 70 HIV positive adults with the aim for n=31 ≥50 years old and n=31 adults with perinatally acquired HIV over the age of 18 years who have completed the study.

6.4. Co-enrolment guidance

Participants should not be participating in any other vaccine study within 30 days prior to enrolment, nor should they co-enrol into any other interventional studies that are deemed to impact on the primary or secondary outcomes for the duration of their participation in the SAGE trial. If they do, they will be omitted from the primary immune analysis.

6.5. Participant Identification and Consent

Potential participants will be identified and approached by their direct healthcare team within their regular outpatient clinic. If interested and agree, the potential participant will be referred to the to the research team for further information and provided with an information sheet. Once the potential participant has had an opportunity to review the information, if they are still interested and consent, they will be booked into a screening visit where written informed consent will be obtained by a trial investigator.

The Principal Investigator (PI) retains overall responsibility for the conduct of research at their site, this includes the taking of informed consent of participants at their site. They must ensure that a delegated medic who is responsible to participate in the informed consent process is duly authorised, trained and competent to participate according to the ethically approved protocol, principles of Good Clinical Practice (GCP) and Declaration of Helsinki.

Written informed consent must be obtained prior to the participant undergoing procedures that are specifically for the purposes of the trial and are out-with standard routine care at the participating site.

6.6. Randomisation Procedure / Code Break

There is no Randomisation.

6.7. Withdrawal of Participants

Participants have the right to withdraw from the study at any time for any reason. The investigator also has the right to withdraw participants from the study drug in the event of inter-current illness, AEs, SAEs, SUSARs, protocol violations, cure, administrative reasons or other reasons. It is understood by all concerned that an excessive rate of withdrawals can render the study un-interpretable; therefore, unnecessary withdrawal of participants should be avoided. Should a participant decide to withdraw from the study, all efforts will be made to report the reason for withdrawal as thoroughly as possible. Should a participant withdraw from study vaccination only, efforts will be made to continue to obtain follow-up data, with the permission of the participant. Any samples and/or data already obtained prior to withdrawal will be used in the analysis.

Participants who wish to withdraw from study vaccination will be asked to confirm whether they are still willing to attend for the subsequent study visits.

To ensure trial endpoints are met, 62 participants will need to have received both injections. The sample size calculations therefore allow for up to 70 participants to be recruited to ensure this occurs. Participants who withdraw prior to their second injection will therefore be replaced up to an including when 62 participants have received 2 vaccinations.

In all cases the date and reasons for withdrawal or withholding the dose of medication will be clearly stated on the participant's CRF. If the reason for removal of a participant from the trial is an adverse event or an abnormal laboratory test result, the principal specific event or test will be recorded on the CRF.

6.8. Expected Duration of Trial

Participants will be on study for approximately 48 weeks, though may be extended due to generous visit window periods. The end of trial will be defined as data lock.

7. Trial Procedures

Table 1 summarises the list of study procedures to be followed during the study visits and at the study conclusion contact. Table 2 summarises study procedures to be performed for the follow-up of each suspected HZ case.

7.1. By Visit

This prospective multicentre study will recruit up to 70 individuals attending HIV services. Individuals will attend for visits at screening, baseline (vaccination), week 4, week 8 (vaccination), week 12, week 24 and week 48. Research and safety bloods will be taken at each visit. Study participants will receive 2 intramuscular doses of HZ/su 2 months apart. Vaccine reactogenicity review will occur 15 minutes post vaccination.
Any individual who develops shingles after vaccination will have swabs taken for viral diagnosis and viral sequencing.

The trial assessment schedule consists of a screening visit (visit 1) followed by an enrolment visit which defines week 0 (visit 2). If preferred by the participant, both visits can occur on the same day.

The first injection will take place at week 0 (visit 2) and the second injection visit is at week 8 (visit 4). Follow-up visits to ask about all adverse events and take blood are at weeks 12, 24 and 48 (visits 5,6,7). Additional visits may be undertaken if indicated, for example to investigate or follow-up an adverse event or abnormal laboratory result or if a participant develops symptoms suggestive of shingles.

The required volumes per visit together with sample collection and processing guidelines are described in detail in the laboratory manual. Required volumes of samples analysed by local laboratories (i.e. safety and HIV parameters) might vary according to local standard procedures. The visit windows are defined in the in Table 1.

Biological samples to be collected: –

Blood samples will be collected from all subjects at every visit to evaluate safety and/or immunogenicity. Should the participant experience a suspected HZ episode, swabs from the lesion and a blood sample will be collected.

Study details: Study subjects will be provided with a subject card which contains the address and telephone number of the main contact for information about the trial. The aim of this card is to inform any physician having to deal with a subject in an emergency situation that the subject is in a clinical trial and that he/she can contact the trial investigator for more relevant information. Subjects must be instructed to keep these cards in their possession at all times.

Study Assessments and Procedures
Refer to the Table 1, for the visit schedule. Note that unscheduled visits may be required. Immediate safety concerns should be addressed by the PI as soon as he or she becomes aware of the concern to determine if the participant should continue or discontinue study vaccination. The PI will inform the Sponsor immediately upon occurrence or awareness. Adherence to the study design requirements, including those specified in the visit schedule, is essential and required for study conduct. All participants will be enrolled and followed up for 48 weeks. The vaccination phase will last 8 approximately weeks.

Procedures prior to study participation

Potential participants will be identified through HIV clinics. Eligible individuals will be informed about the trial and given a patient information sheet at least one day prior to consent is taken which explains the aims, methods, and potential benefits and hazards of the trial.

Screening visit
The study staff conducting the Screening visit will:

- Introduce themselves and their role to the participant and confirm the identity of the participant.
- Confirm that the means of contact is adequate to conduct the contact/visit
- Participants will be provided with the study information, including the participant information sheet (PIS) to read. They will discuss the study with a member of the research team in person or remotely. Consent will be obtained by an investigator.

After informed consent has been collected, a unique trial identifier will be assigned by the study staff. The screening visit will conduct:

- Eligibility assessment (as per inclusion/exclusion criteria)
- Demographics recording
- Medical History
- Vital signs
- Temperature

- Full physical exam
- Urine pregnancy test (women of childbearing potential only)
- Concomitant medications review
- Adverse Events Review

Procedures prior to the first vaccination at enrolment visit

Screening and enrolment can occur on the same day. If not, the enrolment visit should take place within 8 weeks following the screening visit. If more than 8 weeks have elapsed study repeat the screening assessments.

Study staff will review information related to eligibility collected at screening and determine whether there are any clinically relevant abnormalities that require further investigation prior to enrolment.

Baseline, Week 0 (+8 weeks)

The baseline visit will conduct:

- Eligibility Assessment (as per inclusion/exclusion criteria)
- Vital signs
- Temperature
- Directed physical exam
- Concomitant Medication review
- Vaccination
- Vaccine reactogenicity, unsolicited adverse event & IMD review
- Participant survey: beliefs about shingles and shingles vaccines
- Urine pregnancy test (women of childbearing potential only)
- Venepuncture for:
    - CD4 (CD4:CD8)
    - HIV Viral Load
    - Hepatitis BsAg
    - Safety blood sample (FBC, U&E, ALT)
    - Immunology blood sample
    - Serology blood sample

Note: Pregnancy test will be performed even if the subject is menstruating at the time of the study visit. The study vaccine can only be may only be administered if the pregnancy test is negative.

Check contraindications to vaccination: Contraindications to vaccination are to be checked at the beginning of each vaccination visit. Furthermore, any subject with a clinically diagnosed HZ episode between Visit 1 and Visit 2 should receive the second vaccination 3 months after the day of onset of shingles.

Vaccination Visits: 2 (Baseline) & 4

Prior to injection, study staff will conduct an inspection of the site where injections will be administered in each arm as part of the directed physical examination. The axillary, oral or tympanic body temperature of all subjects will be measured prior to any study vaccine administration. The preferred route for recording temperature in this study will be oral. All vaccines may be administered to persons with low-grade fevers, i.e., oral, tympanic on oral setting, or axillary temperature < 37.5°C. If a subject has an axillary/oral/tympanic on oral setting temperature ≥ 37.5°C, it will constitute a contraindication to administration of vaccine.

Study staff should administer the injection into the deltoid muscle of the designated upper arm and record this in the appropriate CRF including the time of injection.

The Shingrix vaccine dose, after reconstitution, is 0.5 ml in volume and should be injected into the deltoid muscle of the non-dominant arm. Following injection participants should remain in clinic, in order to assess vaccine reactogenicity and solicited adverse events at 15 minutes following injection.

If the Investigator or delegate determines that the health on the day of vaccination temporarily precludes vaccination, the visit will be rescheduled within the window period for this visit.

The vaccinees will be observed for 15 minutes, with appropriate medical treatment readily available in case of anaphylaxis, following the administration of vaccine.

All injections will be administered by delegated and suitably trained site staff.

Visit 3, week 4 (+/- 4 weeks)

The following will be conducted:

- Vital signs
- Directed Physical Exam
- Concomitant Medication Review
- Solicited and Unsolicited Adverse Event & IMD Review
- Venepuncture for:
    - Immunology blood sample
    - Serology blood sample

Visit 4, week 8 (-4/+7 weeks)

- Vital signs
- Temperature
- Directed Physical Exam
- Concomitant Medication Review
- Unsolicited Adverse Event & IMD Review
- Urine pregnancy test (women of childbearing potential only)

- Vaccination
- Venepuncture for:
    - Immunology blood sample
    - Serology blood sample

Visit 5, week 12 (+/- 4 weeks)

- Directed Physical Exam
- Concomitant Medication Review
- Solicited and Unsolicited Adverse Event & IMD Review
- Venepuncture for:
    - Immunology blood sample
    - Serology blood sample

Visit 6 week 24 (+/- 4 weeks)

- Directed Physical Exam
- Concomitant Medication Review
- Unsolicited Adverse Event & IMD Review
- Venepuncture for:
    - HIV Viral load
    - Safety blood sample
    - Immunology blood sample
    - Serology blood sample

Visit 7, week 48 (+/- 4 weeks)

- Directed Physical Exam
- Concomitant Medication Review
- Unsolicited Adverse Event & IMD Review
- Venepuncture for:
    - CD4 (CD4:CD8)
    - HIV Viral load
    - Safety blood sample
    - Immunology blood sample
    - Serology blood sample

Participant transfers

It is extremely unlikely that a participant will move from one trial centre to another, but not impossible. In the event that a participant does transfer, a copy of the participant's CRF should be provided to the new site and the participant will need to sign a new consent form. Once this has been done, the new site will take over responsibility for the participant; until this has been done, responsibility for the participant lies with the original site.

Recording of non-serious AEs and SAEs

- Refer to Section 8 for procedures for the Investigator to record AEs and SAEs.
- The subjects will be instructed to contact the investigator immediately should the subject manifest any signs or symptoms they perceive as serious.

Evaluation and confirmation of suspected and confirmed HZ cases

A suspected case of HZ is defined as new unilateral rash accompanied by pain (broadly defined to include allodynia, pruritus or other sensations) and no alternative diagnosis. Subjects clinically diagnosed as having a suspected case of HZ by the investigator will be referred to as a case of 'clinically diagnosed suspected HZ' and followed up.

Determination of confirmed cases of HZ for efficacy analyses is provided by routine clinical PCR. The HZ onset date is the earlier of the following two events: 1) the HZ rash start date; or 2) the date on which pain at the site of a subsequent HZ rash is first noted. The HZ onset date will be confirmed by the investigator and recorded in the eCRF.

Rash lesion samples (two replicate samples on the same day) will be collected from subjects clinically diagnosed as having a suspected case of HZ. If more than one site is involved then swabs needed to be taken from each site – including if systemic symptoms are present, CSF or other bodily fluids).

7.2. Laboratory Tests & Sample Management

Trial safety blood samples (HIV Viral Load, CD4, FBC, U&E's and ALT) will be sent by participating site research teams to their local NHS laboratories for testing and results will be reported via the standard of care pathway.

ACD and SST whole blood research samples will be sent to Imperial College London laboratory for processing (via courier from Guys and St Thomas' NHS Foundation Trust or internal transfer from Imperial College NHS Healthcare Trust), or University of Oxford laboratory (via courier from Oxford University Hospitals NHS Foundation Trust).

Processed samples will then be batch shipped via courier from Imperial College London to the University of Oxford laboratories for analysis: Anti-gE antibody concentrations will be measured by anti-gE enzyme-linked immunosorbent assay. CMI responses will be assessed by intracellular cytokine staining and flow cytometry. In brief, peripheral blood mononuclear cells will be stimulated in vitro with gE peptides, after which frequencies of gE-specific $CD4^+$ T cells expressing at least 2 activation markers (here referred to as $CD4^{2+}$) of the 4 markers assessed (interferon-γ, interleukin 2, tumor necrosis factor–α, and CD40 ligand) were determined. Using hybridization-based methodologies, virus will be purified and sequenced directly from skin lesions.

HZ lesion samples will be analysed for virus using PCR. If virus is detected the second swab will be sent via courier to University College London for viral sequencing. Alternatively, residual DNA from the first swab can also be sent. Any other VZV PCR positive samples (CSF vitreous fluid etc) should also be sent to UCL for sequencing.

Description	Assay location	Tube type	Sample Type
Whole blood collection			
Whole Blood collection: Storage for immunogenicity and Assay	Stored at either Imperial College London or University of Oxford	ACD and SERUM TUBES	PBMC and SERUM
VZV immune response	University of Oxford	ACD	PBMC
VZV antibody	University of Oxford	SST	SERUM
Rash swab Storage for Virological Assay			
Herpes zoster PCR viral load	Clinical site		Viral Swab
Herpes zoster viral sequencing	GOSH/University College London		Swab
Whole blood collection when suspected HZ			
Whole Blood collection: Storage for immunogenicity and Assay	Stored at either Imperial College London or University of Oxford	ACD and SERUM TUBES	PBMC and SERUM
VZV immune response	University of Oxford	ACD	PBMC
VZV antibody	University of Oxford	SST	SERUM

Once analysis has been completed, in the unlikely event any residual samples remain they will be destroyed in accordance with HTA Code of Practice & Laboratory policy.

8. Assessment of Efficacy

8.1. Efficacy Parameters

8.1.1. Primary Efficacy Parameters

1. Total VZV specific cell mediated geometric mean titer (GMT) ratios change from baseline to week 12 (4 weeks after second vaccine dose)
2. Total VZV specific antibody geometric mean titer (GMT) ratios change from baseline to week 12 (4 weeks after second vaccine dose)

8.1.2. Secondary Parameters

1. Change of VZV specific cell mediated mediated geometric mean titer (GMT) ratios change from baseline to week 48
2. Change of VZV specific antibody mediated geometric mean titer (GMT) ratios change from baseline to week 48
3. Occurrence of adverse events of Grade 3 or higher severity
4. Viral sequence of shingles infections

8.1.3 Tertiary Parameters

1. Antigen-specific antibody (Ab) concentrations mediated geometric mean titer (GMT) ratios change from baseline to week 12 (4 weeks after second vaccine dose)in subjects with suspected and confirmed HZ
2. Antigen-specific antibody (Ab) concentrations mediated geometric mean titer (GMT) ratios change from baseline to week 12 (4 weeks after second vaccine dose)in subjects with suspected and confirmed HZ
3. HIV reservoirs will be correlated with Antigen-specific antibody (Ab) concentrations
4. BCR and TCR receptors

8.2. Procedures for Assessing Parameters

Primary and secondary efficacy parameters will be evaluated by venepuncture, to be drawn at week 0,4,8, 12, 24 and 48.

9. Assessment of Safety

9.1. Specification, Timing and Recording of Safety Parameters

The investigator or site staff is/are responsible during the study for the detection and documentation of events meeting the criteria and definition of an adverse event (AE) or serious adverse event (SAE) as provided in this protocol. Each subject will be instructed to contact the investigator immediately should they/the subject manifest any signs or symptoms they perceive as serious.

9.2. Procedures for Recording and Reporting Adverse Events

The Medicines for Human Use (Clinical Trials) Regulations 2004 and Amended Regulations 2006 gives the following definitions:

- Adverse Event (AE): Any untoward medical occurrence in a participant to whom a medicinal product has been administered, including occurrences which are not necessarily caused by or related to that product.
- Adverse Reaction (AR): Any untoward and unintended response in a participant to an investigational medicinal product which is related to any dose administered to that participant.
- Unexpected Adverse Reaction (UAR): An adverse reaction the nature and severity of which is not consistent with the information about the medicinal

product in question set out in the summary of product characteristics (SmPC) for that product (for products with a marketing authorisation)

- Serious adverse Event (SAE), Serious Adverse Reaction (SAR) or Suspected Unexpected Serious Adverse Reaction (SUSAR): Any adverse event, adverse reaction or unexpected adverse reaction, respectively, that:
    - results in death
    - is life-threatening
    - required hospitalisation or prolongation of existing hospitalisation
    - results in persistent or significant disability or incapacity
    - consists of a congenital anomaly or birth defect.

- Important Medical Events (IME) & Pregnancy: Events that may not be immediately life-threatening or result in death or hospitalisation but may jeopardise the participant or may require intervention to prevent one of the other outcomes listed in the definition above should also be considered serious. Although not a serious adverse event, any unplanned pregnancy will also be reported via the SAE reporting system.

- Solicited adverse events: Subjects will be asked to report whether they had any solicited adverse experiences from Day 0 to Day 6 (7-day follow-up period) after each vaccine dose, to the clinical research team. All clinical signs and symptoms will be recorded by the investigator on the appropriate section of the eCRF. The following AEs (Table 3) will be solicited. General AEs are any experiences, which do not occur at the site of injection of a vaccine. They will be recorded as 'general' and include those events.

Table 3 Solicited adverse events

Pain at injection site
Redness at injection site
Swelling at injection site
Fatigue
Fever
† Gastrointestinal symptoms
Headache
Myalgia
Shivering

†Gastrointestinal symptoms include nausea, vomiting, diarrhoea and/or abdominal pain. Please record each symptom as a separate adverse event.

Clinical laboratory parameters and other abnormal assessments qualifying as adverse events or serious adverse events

Abnormal laboratory findings (e.g. clinical chemistry, haematology, urinalysis) or other abnormal assessments that come to the attention of, and are judged by, the

investigator to be clinically significant will be recorded as AEs or SAEs if they meet the definition of an AE.

Reporting Responsibilities

Guy's and St Thomas' NHS Foundation Trust has delegated the delivery of the Sponsor's responsibility for Pharmacovigilance (as defined in Regulation 5 of the Medicines for Human Use (Clinical Trials) Regulations 2004 to the King's Health Partners Clinical Trials Office (KHP-CTO).

Symptoms, adverse events and reactions will be recorded by the research study team. All SAEs, pIMDs SARs and SUSARs (except those specified in this protocol as not requiring reporting) will be reported immediately (and certainly no later than 24hrs) by the Investigator to the KHP-CTO and CI for review in accordance with the current Pharmacovigilance Policy. Guidance for SAE reporting can be found at: https://khpcto.co.uk/SAEs/SAE_Reporting.php.

The SmPC with current regulatory approval for the trial will be used by the Investigator (or delegate) to assess SAE reports to identify SUSARs.

The KHP-CTO will maintain an SAE tracking database of all events reported. The KHP-CTO will report SUSARs to the regulatory authorities (MHRA, competent authorities of other EEA (European Economic Area) states) in which the trial is taking place.
The Chief Investigator will report to the relevant ethics committee. Reporting timelines are as follows:

- SUSARs which are fatal or life-threatening must be reported not later than 7 days after the sponsor is first aware of the reaction. Any additional relevant information must be reported within a further 8 days
- SUSARs that are not fatal or life-threatening must be reported within 15 days of the sponsor first becoming aware of the reaction.

The Chief Investigator and KHP-CTO (on behalf of the sponsor), will submit a Development Safety Update Report (DSUR) relating to this trial IMP, to the MHRA and REC annually.

Causality

The investigator must assess the causality of all events or reactions in relation to the trial therapy using the definitions in Table 6. There are five categories: unrelated, unlikely, possible, probable, and definite. If the causality assessment is unrelated or unlikely to be related, the event is classified as an S/AE. If the causality is assessed as possible, probable or definitely related, then the event is classified as an S/AR

Potential immune-mediated diseases:

Potential immune-mediated diseases (pIMDs) are a subset of AESI that include autoimmune diseases and other inflammatory and/or neurologic disorders of interest which may or may not have an autoimmune aetiology. The list pIMDs include those listed in the Table 4.

However, the investigator will exercise his/her medical and scientific judgement in deciding whether other diseases have an autoimmune origin (that is, pathophysiology involving systemic or organ-specific pathogenic autoantibodies) and should also be recorded as a pIMD.

Although they may not necessarily fit the criteria of a Serious Adverse Event, for the purposes of this trial, any pIMD will also be reported via the SAE reporting system (selecting “IME” option in Section 9). As part of the pIMD reporting, the following should be included in Section 10 of the SAE form:

- Criteria: pIMD
- Severity: mild, moderate, severe, n/a
- Dose number: 1, 2.

Table 4 Potential immune-mediated diseases (pIMDs)

Medical Concept	Additional Notes
Blood disorders and coagulopathies	
Antiphospholipid syndrome	
Autoimmune aplastic anemia	
Autoimmune hemolytic anemia	• Includes warm antibody hemolytic anemia and cold antibody hemolytic anemia
Autoimmune lymphoproliferative syndrome (ALPS)	
Autoimmune neutropenia	
Autoimmune pancytopenia	
Autoimmune thrombocytopenia	
Evans syndrome	
Pernicious anemia	
Thrombosis with thrombocytopenia syndrome (TTS)	
Thrombotic thrombocytopenic purpura	
Cardio-pulmonary inflammatory disorders	
Idiopathic Myocarditis/Pericarditis	• Autoimmune / Immune-mediated myocarditis • Autoimmune / Immune-mediated pericarditis • Giant cell myocarditis
Idiopathic pulmonary fibrosis	Including but not limited to: • Idiopathic interstitial pneumonia (frequently used related terms include “Interstitial lung disease”, “Pulmonary fibrosis”, “Immune-mediated pneumonitis”)
Pulmonary alveolar proteinosis (PAP)	
Pleuroparenchymal fibroelastosis (PPFE)	
Endocrine disorders	
Addison’s disease	
Autoimmune / Immune-mediated thyroiditis	Including but not limited to: • Hashimoto thyroiditis (autoimmune hypothyroidism, lymphocytic thyroiditis) • Atrophic thyroiditis • Silent thyroiditis • Thyrotoxicosis
Autoimmune diseases of the testis and ovary	
Autoimmune hyperlipidemia	
Autoimmune hypophysitis	
Diabetes mellitus type I	

Medical Concept	Additional Notes
Grave's or Basedow's disease	• Includes Marine Lenhart syndrome and Graves' ophthalmopathy, also known as thyroid eye disease (TED) or endocrine ophthalmopathy
Insulin autoimmune syndrome	
Polyglandular autoimmune syndrome	• Includes Polyglandular autoimmune syndrome type I, II and III
Eye disorders	
Ocular Autoimmune / Immune-mediated disorders	Including but not limited to: • Acute macular neuroretinopathy (also known as acute macular outer retinopathy) • Autoimmune / Immune-mediated retinopathy • Autoimmune / Immune-mediated uveitis, including idiopathic uveitis and sympathetic ophthalmia • Cogan's syndrome: an oculo-audiovestibular disease • Ocular pemphigoid • Ulcerative keratitis • Vogt-Koyanagi-Harada disease
Gastrointestinal disorders	
Autoimmune / Immune-mediated pancreatitis	
Celiac disease	
Inflammatory Bowel disease	Including but not limited to: • Crohn's disease • Microscopic colitis • Terminal ileitis • Ulcerative colitis • Ulcerative proctitis
Hepatobiliary disorders	
Autoimmune cholangitis	
Autoimmune hepatitis	
Primary biliary cirrhosis	
Primary sclerosing cholangitis	
Musculoskeletal and connective tissue disorders	
Gout	• Includes gouty arthritis
Idiopathic inflammatory myopathies	Including but not limited to: • Dermatomyositis • Inclusion body myositis • Immune-mediated necrotizing myopathy • Polymyositis
Mixed connective tissue disorder	
Polymyalgia rheumatica (PMR)	
Psoriatic arthritis (PsA)	

Medical Concept	Additional Notes
Relapsing polychondritis	
Rheumatoid arthritis	Including but not limited to: • Rheumatoid arthritis associated conditions • Juvenile idiopathic arthritis • Palindromic rheumatism • Still's disease • Felty's syndrome
Sjögren's syndrome	
Spondyloarthritis	Including but not limited to: • Ankylosing spondylitis • Juvenile spondyloarthritis • Keratoderma blenorrhagica • Psoriatic spondylitis • Reactive Arthritis (Reiter's Syndrome) • Undifferentiated spondyloarthritis
Systemic Lupus Erythematosus	• Includes Lupus associated conditions (e.g. Cutaneous lupus erythematosus, Lupus nephritis, etc.) or complications such as shrinking lung syndrome (SLS)
Systemic Scleroderma (Systemic Sclerosis)	• Includes Reynolds syndrome (RS), systemic sclerosis with diffuse scleroderma and systemic sclerosis with limited scleroderma (also known as CREST syndrome)
Neuroinflammatory/neuromuscular disorders	
Acute disseminated encephalomyelitis (ADEM) and other inflammatory-demyelinating variants	Includes the following: • Acute necrotising myelitis • Bickerstaff's brainstem encephalitis • Disseminated necrotizing leukoencephalopathy (also known as Weston-Hurst syndrome, acute hemorrhagic leuko-encephalitis, or acute necrotizing hemorrhagic encephalomyelitis) • Myelin oligodendrocyte glycoprotein antibody-associated disease • Neuromyelitis optica (also known as Devic's disease) • Noninfective encephalitis / encephalomyelitis / myelitis • Postimmunization encephalomyelitis
Guillain-Barré syndrome (GBS)	• Includes variants such as Miller Fisher syndrome and the acute motor and sensory axonal neuropathy (AMSAN)
Idiopathic cranial nerve palsies/paresis and inflammations (neuritis)	Including but not limited to: • Cranial nerve neuritis (e.g. Optic neuritis) • Idiopathic nerve palsies/paresis (e.g. Bell's palsy) • Melkersson-Rosenthal syndrome • Multiple cranial nerve palsies/paresis
Multiple Sclerosis (MS)	Includes the following: • Clinically isolated syndrome (CIS) • Malignant MS (the Marburg type of MS)

Medical Concept	Additional Notes
	• Primary-progressive MS (PPMS) • Radiologically isolated syndrome (RIS) • Relapsing-remitting MS (RRMS) • Secondary-progressive MS (SPMS) • Uhthoff's phenomenon
Myasthenia gravis	• Includes ocular myasthenia and Lambert-Eaton myasthenic syndrome
Narcolepsy	• Includes narcolepsy with or without presence of unambiguous cataplexy
Peripheral inflammatory demyelinating neuropathies and plexopathies	Including but not limited to: • Acute Brachial Radiculitis (also known as Parsonage-Turner Syndrome or neuralgic amyotrophy) • Antibody-mediated demyelinating neuropathy • Chronic idiopathic axonal polyneuropathy (CIAP) • Chronic Inflammatory Demyelinating Polyradiculoneuropathy (CIDP), including atypical CIDP variants (e.g. multifocal acquired demyelinating sensory and motor neuropathy also known as Lewis-Sumner syndrome) • Multifocal motor neuropathy (MMN)
Transverse myelitis (TM)	• Includes acute partial transverse myelitis (APTM) and acute complete transverse myelitis (ACTM)
Renal disorders	
Autoimmune / Immune-mediated glomerulonephritis	Including but not limited to: • IgA nephropathy • IgM nephropathy • C1q nephropathy • Fibrillary glomerulonephritis • Anti-glomerular basement membrane disease • Glomerulonephritis rapidly progressive • Membranoproliferative glomerulonephritis • Membranous glomerulonephritis • Mesangioproliferative glomerulonephritis • Tubulointerstitial nephritis and uveitis syndrome
Skin and subcutaneous tissue disorders	
Alopecia areata	
Autoimmune / Immune-mediated blistering dermatoses	Including but not limited to: • Bullous Dermatitis • Bullous Pemphigoid • Dermatitis herpetiformis • Epidermolysis bullosa acquisita (EBA) • Linear IgA-mediated bullous dermatosis (LABD), also known as Linear IgA disease • Pemphigus
Erythema multiforme	

Medical Concept	Additional Notes
Erythema nodosum	
Interstitial granulomatous dermatitis	
Lichen planus	• Includes liquen planopilaris
Localised Scleroderma (Morphoea)	• Includes Eosinophilic fasciitis (also called Shulman syndrome)
Palisaded neutrophilic granulomatous dermatitis	
Psoriasis	
Pyoderma gangrenosum	
Stevens-Johnson Syndrome (SJS)	Including but not limited to: • Toxic Epidermal Necrolysis (TEN) • SJS-TEN overlap
Sweet's syndrome	• Includes Acute febrile neutrophilic dermatosis
Vitiligo	
Vasculitis	
Large vessels vasculitis	Including but not limited to: • Arteritic anterior ischemic optic neuropathy (AAION or arteritic AION) • Giant cell arteritis (also called temporal arteritis) • Takayasu's arteritis
Medium sized and/or small vessels vasculitis	Including but not limited to: • Anti-neutrophil cytoplasmic antibody (ANCA) positive vasculitis (type unspecified) • Behcet's syndrome • Buerger's disease (thromboangiitis obliterans) • Churg–Strauss syndrome (allergic granulomatous angiitis) • Erythema induratum (also known as nodular vasculitis) • Henoch-Schonlein purpura (also known as IgA vasculitis) • Microscopic polyangiitis • Necrotizing vasculitis • Polyarteritis nodosa • Single organ cutaneous vasculitis, including leukocytoclastic vasculitis, hypersensitivity vasculitis and acute hemorrhagic edema of infancy (AHEI) • Wegener's granulomatosis
Other (including multisystemic)	
Anti-synthetase syndrome	
Capillary leak syndrome	
Goodpasture syndrome	
Immune-mediated enhancement of disease	• Includes vaccine associated enhanced disease (VAED and VAERD). Frequently used related terms include "vaccine-mediated enhanced disease (VMED)", "enhanced respiratory disease (ERD)", "vaccine-induced enhancement of infection", "disease enhancement", "immune enhancement", and "antibody-dependent enhancement (ADE)

Medical Concept	Additional Notes
Immunoglobulin G4 related disease	
Langerhans' cell histiocytosis	
Multisystem inflammatory syndromes	Including but not limited to: • Kawasaki's disease • Multisystem inflammatory syndrome in adults (MIS-A) • Multisystem inflammatory syndrome in children (MIS-C)
Overlap syndrome	
Pulmonary renal syndrome	
Raynaud's phenomenon	
Sarcoidosis	• Includes Loefgren syndrome
Susac's syndrome	

Table 6 : Assigning Type of S/AE Through Causality

RELATIONSHIP	DESCRIPTION	S/AE TYPE
Definite	There is clear evidence to suggest a causal relationship and other possible contributing factors can be ruled out.	S/AR
Probable	There is evidence to suggest a causal relationship and the influence of other factors is unlikely.	S/AR
Possible	There is some evidence to suggest a causal relationship (for example, because the event occurs within a reasonable time after administration of the trial medication). However, the influence of other factors may have contributed to the event (for example, the participant's clinical condition, other concomitant treatments).	S/AR
Unlikely	There is little evidence to suggest that there is a causal relationship (for example, the event did not occur within a reasonable time after administration of the trial medication). There is another reasonable explanation for the event (for example, the participant's clinical condition, other concomitant treatment).	Unrelated S/AE
Unrelated	There is no evidence of any causal relationship	Unrelated S/AE

9.3. Protocol vaccine discontinuation

In consenting to the trial, participants are consenting to receive vaccines, to attend the visits for trial follow-up and to provide information that supports data collection.

An individual participant may stop injections early or be stopped early for any of the following reasons:

- Pregnancy in the participant
- Unacceptable toxicity that precludes further injections
- Intercurrent illness that prevents further injections including emergent conditions that meet the exclusion criteria
- Withdrawal of consent for injections by the participant

A decision to discontinue further injections should be taken in consultation with the local PI.

9.4. Adverse events that do not require reporting

All Adverse Events will be recorded by the research staff. These can be extracted from the CSAM MedSciNet database as a list of events with onset and end dates.

9.5. Premature Termination of the Trial

The trial may be prematurely discontinued by the Sponsor, Chief Investigator or Regulatory Authority based on new safety information or for other reasons given by the Data Monitoring & Ethics Committee/ Regulatory Authority or ethics committee concerned.
If the trial is prematurely discontinued, active participants will be informed and no further participant data will be collected. The Competent Authority and Research Ethics Committee will be informed within 15 days of the early termination of the trial.

10. Statistics

10.1. Sample Size

The two study groups (PLWH aged ≥50 years, and young adults with perinatally acquired HIV infection) will be considered and analysed separately. Therefore, the sample size described below will be obtained in each patient population.

This is a single arm study which aims to precisely estimate the average change at 12 weeks in (i) VZV specific antibody and (ii) T cell responses. The precision of the population estimates will be quantified using 95% confidence intervals (CI). Therefore, the sample size calculations are performed to ensure the width of the CIs are sufficiently narrow. The acceptable level of precision was derived using clinical judgment of a meaningful change, alongside practical considerations on participant recruitment numbers.

Due to their anticipated log-normal distribution, the primary study endpoints will both be summarised using geometric means. As this is equivalent to calculating the [arithmetic] mean of the natural logathithm titer values (followed by back-transformation to the original scale), calculations are presented here on the natural

logarithm scale. Note that the results will be presented in study reports after back-transformation to the original scale:

1. Total VZV specific cell mediated geometric mean titer (GMT) ratios change from baseline to week 12 (4 weeks after second vaccine dose)

A previous study by Benson et al of the Zostavax vaccine reported a geometric mean fold-change at 12 weeks of 3.8. This corresponds to an absolute change on the natural log scale of 1.33. The corresponding standard deviation was also derived from this study and conservatively rounded up to 3.4. A confidence interval width of 3 $\log_e 5x10^5$ cells was chosen as an acceptable level of precision. The probability was set at 90% (analogous to a study power: there is a 90% chance that the CI will be no wider than 0.6 in a future study). Based on these assumptions, we will have 90% probability of estimating the mean to a precision of 3 (the 95% confidence interval will have a width of ±1.5) with a sample size **of 30 individuals** (Stata, Version 16: command used ciwidth onemean, w(3) probwidth(0.9) sd(3.4)).

2.Total VZV specific antibody geometric mean titer (GMT) ratios change from baseline to week 12 (4 weeks after second vaccine dose)

Benson et al reported a geometric mean fold-change at 12 weeks of 1.80. This corresponds to an absolute change on the natural log scale of 0.59. The corresponding standard deviation was derived from this study and conservatively rounded up to 0.7. A confidence interval width of 0.6 $\log_e 5x10^5$ cells was chosen as an acceptable level of precision. Based on these assumptions, we will have 90% probability of estimating the mean to a precision of 0.6 with a sample size **of 31 individuals** (Stata, Version 16: command used ciwidth onemean, w(0.6) probwidth(0.9) sd(0.7)).

To end up with 61 evaluable participants, we will recruit 70 individuals: approximately 35 in each group.
We acknowledge only common adverse events will be identified in this study, due to the relatively small study sample size. However, other studies of this licenced vaccine have studied safety in great detail.

10.2. Randomisation

No randomisation

10.3. Analysis

The analysis approach described below will be undertaken for both patient populations (PLWH aged ≥50 and young adults with perinatally acquired infection). All continuous measures will be assessed for Normality, and we will apply a suitable transformation if appropriate (for example, by taking natural logarithms).

Primary endpoints:

1. ***Total VZV specific cell mediated titer change change from baseline to week 12 (4 weeks after second vaccine dose).***
   The individual values at baseline and week 12 will be presented on a dot plot. The values will be summarised as the geometric mean titer (GMT) ratio and its corresponding 95% confidence interval

2. ***Total VZV specific antibody titer change from baseline to week 12 (4 weeks after second vaccine dose)***
   The individual values at baseline and week 12 will be presented on a dot plot. The values will be summarised as the geometric mean titer (GMT) ratio and its corresponding 95% confidence interval

Secondary endpoints

3. ***Change of VZV specific cell mediated titer change from baseline to week 48***
   The individual values at baseline and week 48 will be presented on a dot plot. The values will be summarised as the geometric mean titer (GMT) ratio and its corresponding 95% confidence interval

4. ***Change of VZV specific antibody titer change from baseline to week 48***
   The individual values at baseline and week 48 will be presented on a dot plot. The values will be summarised as the geometric mean titer (GMT) ratio and its corresponding 95% confidence interval

5. ***Occurrence of adverse events (fatal and non-fatal, of all grades)***

   All AEs will be reported. The number and percentage with an adverse event and their severity will be presented in frequency tables. The number and percentage of participants reporting each solicited local and solicited systemic AE during the solicited 7-day follow-up period will be tabulated with exact 95% CIs after each vaccination visit and overall per participant

   The duration of the solicited AEs, both local (for each vaccine separately) and systemic, during the 7-day follow-up period after each vaccination visit and overall

   The number and percentage of participants reporting unsolicited AEs classified by MedDRA primary System Organ Class (SOC) and Preferred Term (PT) will be summarized along with exact 95% CIs following vaccination. This will be the same for SAEs & pIMDs.

6. ***Viral sequence of shingles infections***

Genome sequencing of confirmed HZ cases will be described to understand why breakthrough infection occurred.

8.1.3 Tertiary Parameters

Antigen-specific antibody (Ab) concentrations mediated geometric mean titer (GMT) ratios change from baseline to week 12 (4 weeks after second vaccine dose)in subjects with suspected and confirmed HZ and antigen-specific antibody (Ab) concentrations mediated geometric mean titer (GMT) ratios change from baseline to week 12 (4 weeks after second vaccine dose)in subjects with suspected and confirmed HZ will be analysed.

We will summarize Anti-gE antibody concentrations expressed as GMC with 95% CI at each timepoint. GMC calculations will be performed by taking the anti-log of the mean of the log concentration transformations. Next, the change of T cell response and the outcome of VZV antibody titre over the five study time points will be described.

Genome sequencing of confirmed HZ cases will be described to understand why breakthrough infection occurred. HIV reservoirs will be correlated with antibody specific and cell mediated GMT ratios.

BCR and TCR receptor repertoires will be described and correlated with immunogenicity.

Limitations

The study is not powered to assess clinical protection but is designed to determine safety and immunogenicity in previously unresearched groups. This is the first investigation of shingles vaccination in individuals with perinatally acquired HIV infection. Results will be used to inform national guidelines.

11. Trial Steering Committee

A Trial Steering Committee (TSC) is not required as this is not an efficacy study and the safety profile is known. The Trial Management Group (TMG) will fulfil the role of safety oversight.

12. Data Monitoring Committee

An Independent Data Monitoring Committee (IDMC) is not required for this trial. This is a well-known, well tolerated vaccine that has been given to HIV positive and negative people as routine care in many countries including the USA. There is no interim analysis of endpoints.

13. Direct Access to Source Data and Documents

The Investigator(s) will permit trial-related monitoring, audits, REC review, and regulatory inspections by providing the Sponsor, Regulators and REC direct access to source data and other documents. It is anticipated that during the current epidemic most monitoring will be remote however onsite visits will be conducted as required by the Sponsor.

14. Ethics & Regulatory Approvals

The trial will be conducted in compliance with the principles of the Declaration of Helsinki (1996), the principles of GCP and in accordance with all applicable regulatory requirements including but not limited to the Research Governance Framework and the Medicines for Human Use (Clinical Trial) Regulations 2004, as amended in 2006 and any subsequent amendments.

This protocol and related documents, and any subsequent amendments will be submitted for combined review to Health Research Authority (HRA), Research Ethics Committee (REC), and includes the Medicines and Healthcare products Regulatory Agency (MHRA) for Clinical Trial Authorisation.
The trial will not commence until appropriate confirmation of capacity and capability is in place for each participating hospital site and KHPCTO has issued “greenlight”.

The Chief Investigator will submit a final report at conclusion of the trial to the KHP-CTO (on behalf of the Sponsor) and the REC within the timelines defined in the Regulations. The KHP-CTO or delegate will upload the final report to MHRA on behalf of the Sponsor.

15. Quality Assurance

Monitoring of this trial will be to ensure compliance with Good Clinical Practice and scientific integrity will be managed and oversight retained, by the KHP-CTO Quality Team. The fingerpick blood sampling and posting has been validated for taking serum for HIV testing. To ensure that participants take the sample correctly and take enough blood they will receive guidance by the research team through phone call and video calling.

16. Data Handling

The Chief Investigator will act as custodian for the trial data. The following guidelines will be strictly adhered to:

- Information with regards to study participants will be kept confidential and managed in accordance with the General Data Protection Regulation, NHS Caldicott Guardian, UK Policy Framework for Health and Social Care Research and Research Ethics Committee Approval.
- The CI and the study team will adhere to these parameters to ensure that the Participant’s identity is protected at every stage of their participation within the study. To ensure this is done accordingly, at time of pre-screening and consent,

each participant will be allocated a unique screening number by the CSAM MedSciNet database, and a site and subject specific enrolment number will be allocated if the participant is randomised into the study.

- Fully anonymised data will be shared with fellow researchers via conference presentation and via publication of the results in scientific journals.
- All trial data will be stored in line with the Medicines for Human Use (Clinical Trials) Amended Regulations 2006 and the Data Protection Act and archived in line with the Medicines for Human Use (Clinical Trials) Amended Regulations 2006 as defined in the Kings Health Partners Clinical Trials Office Archiving SOP.
- Direct access will be granted to authorised representatives from the Sponsor, host institution and the regulatory authorities to permit trial-related monitoring, audits and inspections. Access will be approved by the participant giving written informed consent.

17. Data Management

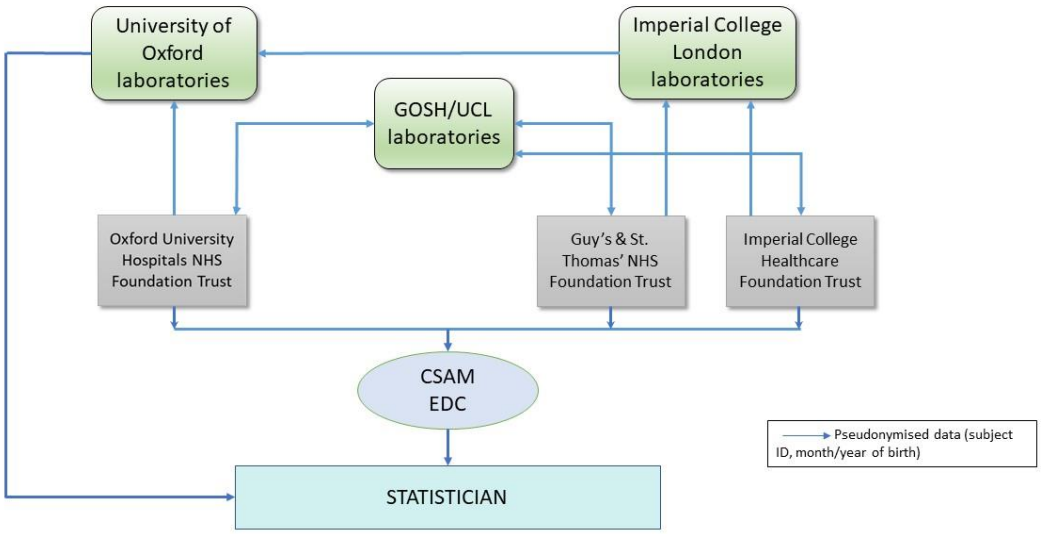
Trial data will be collected on the electronic CSAM MedSciNet database using Case Report Forms (CRFs), designed in CSAM MedSciNet, and approved by the CI, trial statistician and Sponsor. Participants will be provided with a copy of their completed consent form for their records, and they will be provided with a leaflet containing details about the study. The CSAM MedSciNet database will only be accessed by trained and authorised users, as recorded on the site and central delegation logs, and approved by the CI/PI. Each user will be assigned specific user roles and rights. Sponsor representatives and statistician will have read-only access to the data. The study research team will have access to complete the following CRFs; eligibility confirmation and, prescription form, and SAE report. The PI/CI will have overall responsibility for data captured in the eCRF and be able to review, lock and electronically sign the completed eCRFs.

Source data will be defined on the source data location list and will include patient notes, including electronic patient notes. The study data will be collected in the CSAM MedSciNet eCRF which will be validated and approved for accurate data collection, and version controlled. CSAM MedSciNet user accounts will be set up for research sites and central teams (trial statistician) with specific roles and rights, and data access rights as defined in the User Requirements Specification documents and approved by the CI.

In the eCRF, repetitive data such as protocol reference, subject ID, and patient initials can be duplicated on the relevant CRFs automatically, ensuring no duplication of CRF pages and data accuracy. The CSAM MedSciNet eCRF will have built-in edit checks and validations tagged to each data field as well as to the CRF as a whole. Therefore, the majority of data cleaning activities will take place during the completion of the eCRFs, and the dataflow query process enable queries and data clarifications in real time on the data. The inbuilt audit trail function will maintain a record of data edits and amendments. All eCRFs will be available for monitoring by the sponsor monitors, and both teams will have read-only access to the study data. Completed CRFs with study data and study database extracts can be downloaded for study archiving. Central study documents will be filed in the study TMF.

After data lock, data sets will be transferred via secure encrypted email to the statistician for analysis and held securely on University College London network. Once analysis is complete, data sets will be transferred back to Sponsor. All datasets will be fully anonymised.

SAGE DATA FLOW DIAGRAM



18. Publication Policy

It is intended that the results of the study will be reported and disseminated at international conferences and in peer-reviewed scientific journals. The final study report, and related publications, will be authored in line with the arrangements set out under normal Sponsorship arrangements. All publications will be approved by the Chief Investigator. Authorship will follow the criteria established by the International Committee of Medical Journal Editors.

19. Insurance / Indemnity

The Sponsor's NHS indemnity scheme applies.

20. Financial Aspects

Funding to conduct the trial is provided by GSK.

21. Archiving

At the end of this trial, all trial data will be stored in line with the Medicines for Human Use (Clinical Trials) Amended Regulations 2006 and the 2018 Data Protection Act and archived in line with the Medicines for Human Use (Clinical Trials) Amended Regulations 2006 as defined in the Sponsor Archiving Standard Operating Procedure (SOP).

22. Signatures

_____	_____
Chief Investigator	Date
Print name	

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Herpes Zoster Zostavax Recommendations and Vaccine Specifics | CDC

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