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A phase 1 dose escalation open label trial to assess safety and immunogenicity of candidate ChAdOx1- and MVA-vectored conserved mosaic HIV-1 vaccines, given sequentially to healthy HIV-1/2-negative adult volunteers in Oxford, UK

Study Reference: HIV-CORE 0052

Protocol Version: 6.0

Date: 27Jan2022

Chief Investigator: Dr Paola Cicconi

Non-Clinical Principal Investigator: Prof Tomáš Hanke

Sponsor: University of Oxford

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IRAS project ID: 273882

JENNER VACCINE TRIALS
NUFFIELD DEPARTMENT OF MEDICINE

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Full Study Title	A phase 1 dose escalation open label trial to assess safety and immunogenicity of candidate ChAdOx1- and MVA-vectored conserved mosaic HIV-1 vaccines, given sequentially to healthy HIV-1/2-negative adult volunteers in Oxford, UK **Study Code**: HIV-CORE 0052 **EudraCT Number**: 2019-003973-25 **IRAS project ID**: 273882
Chief Investigator	**Dr Paola Cicconi** Centre for Clinical Vaccinology and Tropical Medicine University of Oxford, Churchill Hospital, Old Road, Headington Oxford, OX3 7LE Email: paola.cicconi@ndm.ox.ac.uk
Non-Clinical Principal Investigator	**Professor Tomáš Hanke** The Jenner Institute, University of Oxford Old Road Campus Research Building, Roosevelt Drive Oxford, OX3 7DQ Tel: 01865 617630 Email: tomas.hanke@ndm.ox.ac.uk
Trial Sites	**Centre for Clinical Vaccinology and Tropical Medicine (CCVTM)** Churchill Hospital, Old Road, Headington Oxford, OX3 7LE
Sponsor/Monitor	**University of Oxford** Clinical Trials and Research Governance Level 1 Boundary Brook House, Old Road, Headington Oxford, OX3 7GB Tel: 01865 616480 Email: ctrg@admin.ox.ac.uk
Local Safety Monitor	**Dr Brian Angus** Centre for Clinical Vaccinology and Tropical Medicine Churchill Hospital, Old Road, Headington Oxford, OX3 7LE Tel: 01865 220289 Email: brian.angus@ndm.ox.ac.uk

Confidentiality Statement

This document contains confidential information that must not be disclosed to anyone other than the Sponsor, the Investigator Team, HRA, host organisation, and members of the Research Ethics Committee and other regulatory bodies. This information cannot be used for any purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of Dr Paola Cicconi and Prof Tomáš Hanke.

Statement of Compliance

The trial will be conducted in compliance with the protocol, the principles of Good Clinical Practice, Medicines for Human Use (Clinical Trial) Regulations 2019 (as amended) and all other applicable regulatory requirements.

Chief Investigator and Non-Clinical Principal Investigator approval and agreement

I hereby approve this version of the protocol and declare no conflict of interest:

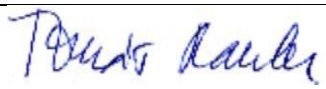
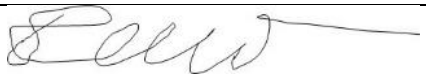
Name	**Signature**	**Date**
Tomáš Hanke		28Jan2022
Paola Cicconi		28Jan2022

Table of Contents

1. SYNOPSIS

Title	A phase 1 dose escalation open label trial to assess safety and immunogenicity of candidate ChAdOx1- and MVA-vectored conserved mosaic HIV-1 vaccines given sequentially to healthy HIV-1/2-negative adult volunteers in Oxford, UK
Trial Identifier	HIV-CORE 0052
Trial Centres	Centre for Clinical Vaccinology & Tropical Medicine, University of Oxford, Churchill Hospital, Old Road, Headington, Oxford, OX3 7LE
Clinical Phase	1
Design	Open label
Population	HIV-1/2-negative, low-risk males and females 18-65 years of age
Study design	<table><tr><th>Group</th><th>N</th><th>Wk 0</th><th>Wk 4</th></tr><tr><td>**1**</td><td>**3**</td><td>**C1 (low dose)**</td><td>**-**</td></tr><tr><td>**2**</td><td>**10**</td><td>**C1 (high dose)**</td><td>**M3M4**</td></tr><tr><td>Total</td><td>**13**</td><td></td><td></td></tr></table> C1; ChAdOx1.tHIVconsv1 M3; MVA.tHIVconsv3 M4; MVA.tHIVconsv4
Visit Schedule	**GROUP 1** Seven visits over 4 months; screening, **D0 (C1 low-dose vaccination**), D1, D7, D14 (phone call only), D28, D112.

GROUP 2 Twelve visits over 5 months; screening, **D0 (C1 vaccination)**, D1, D7, D14 (phone call only), **D28**, **(M3M4 vaccination)**, D29, D35, D42, D56, D84, D140

Planned Trial Period	Q2 2021 – Q2 2022

Objectives

PRIMARY

Safety

- To evaluate the safety and tolerability of ChAdOx1.tHIVconsv1 given alone and in a prime boost vaccine regimen followed by MVA.tHIVconsv3 & 4 in HIV-1/2-negative healthy adults.

SECONDARY

- To determine the proportion of vaccine recipients who developed tHIVconsvX-specific T-cell responses induced by the ChAdOx1.tHIVconsv1 followed by MVA.tHIVconsv3 & 4 vaccines.
- To assess the tHIVconsvX-specific T-cell responses of for their frequency, breadth and duration in vaccine responders.
- To assess ability of the tHIVconsvX-specific T-cell responses to inhibit replication *in vitro* of viruses of four major HIV-1 clades A, B, C and D.

EXPLORATORY

- To assess the plurifunctionality of the tHIVconsvX-specific T-cells in the vaccine responders.
- To characterise the gut microbiome composition and richness.

Endpoints	**PRIMARY** ***Safety*** • Proportion of volunteers with local and systemic reactogenicity events from Day 0 to Day 6 post vaccination • Proportion of volunteers with Grade 3 or 4 unsolicited adverse events (AEs) through 28 days post final vaccination • Proportion of volunteers with vaccine related serious adverse events (SAEs) collected throughout the study period **SECONDARY** • Proportion of vaccine recipients developing HIV-1-specific T-cell responses • Frequency, breadth and duration of the tHIVconsvX-specific T-cell responses to conserved epitopes measured in IFN-γ ELISpot assay in each vaccine recipient • Breadth of inhibition of HIV-1 viruses *in vitro* **EXPLORATORY** • Proportions of mono-, bi- and tri-functional tHIVconsvX-specific T-cells in the vaccine recipients • Shotgun sequencing and metabolomics analyses.
Investigational products	• The ChAdOx1.tHIVconsv1 vaccine utilises non-replicating engineered simian adenovirus vaccine vector ChAdOx1 to deliver a mosaic immunogen tHIVconsv1 derived from functionally conserved regions of HIV-1 proteins. • Two vaccine components MVA.tHIVconsv3 and MVA.tHIVconsv4 complement each other and will be used as a pair for immunisations. They utilise non-replicating poxvirus MVA delivering bi-valent mosaic

	immunogens, either tHIVconsv3 or tHIVconsv4, derived from functionally conserved regions of HIV-1 proteins.
Formulation	Suspension (all finished products)
Route of Administration	Intramuscularly (IM), into the deltoid region of each arm
Dose per Administration	• 5.0 x 10^9 vp of ChAdOx1.tHIVconsv1 (C1 low dose half a dose to be administered to each arm) • 5.0 x 10^{10} vp of ChAdOx1.tHIVconsv1 (C1 high dose half a dose to be administered to each arm) • 1.0 x 10^8 pfu of MVA.tHIVconsv3 (M3) left arm • 0.9 x 10^8 pfu of MVA.tHIVconsv4 (M4) right arm

2. ABBREVIATIONS

AE	Adverse event
AIDS	Acquired Immunodeficiency Syndrome
ART	Antiretroviral treatment
AR	Adverse reaction
CCVTM	Centre for Clinical Vaccinology and Tropical Medicine
CEF	Chick Embryo Fibroblasts
ChAdV63	Vaccine vector derived from simian adenovirus serotype 63
ChAdOx1	Vaccine vector derived from simian adenovirus serotype Y25
CI	Chief Investigator
CRF	Case Report Form
CTL	Cytotoxic T-Lymphocyte
CTRG	Clinical Trials and Research Governance
DNA	2'-deoxyribonucleic acid
DSUR	Development Safety Update Report
ELISA	Enzyme linked immunosorbent assay
ELISpot	Enzyme linked immunospot assay
GCP	Good Clinical Practice
GMO	Genetically modified organism
GP	General Practitioner
HBsAg	Hepatitis B Surface Antigen
HIV	Human Immunodeficiency Virus
HIV-1	Human Immunodeficiency Virus type 1
HIV-1/2	Human Immunodeficiency Virus type 1/2
IB	Investigator's Brochure
ICF	Informed Consent Form
IMP	Investigational Medicinal Product
LSM	Local safety monitor
MHRA	Medicines and Healthcare products Regulatory Agency
MVA	Modified Vaccinia Ankara
PI	Principal Investigator
PIS	Participant Information Sheet
pfu	Plaque forming unit
REC	Research Ethics Committee
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SOP	Standard Operating Procedure
SUSAR	Suspected Unexpected Serious Adverse Reactions
TMF	Trial Master File
vp	Viral particle

3. BACKGROUND AND RATIONALE

3.1. Urgent need for a vaccine against HIV infection/AIDS

Control of the HIV epidemic remains one of the global health priorities. Despite remarkable progress achieved in decreasing HIV transmission and AIDS-related deaths in the last decade due to the development of over 30 antiretroviral drugs, HIV continues to spread, infecting approximately 1.8 million people in 2016[(1)]. Around a third of people who are HIV positive do not know their status and hence do not receive treatment[(1)]. For those who know their status, antiretroviral drugs may not be available on a regular reliable basis in many resource-poor settings[(2)]. In addition to that, they have long-term side effects, their effective use requires rigorous daily compliance[(3)] and the circulating and/or transmitted viruses have been shown to develop resistance to several antiretroviral drugs. Also, there is unwillingness to take drugs in a surprisingly large proportion of infected individuals, even in the USA[(4)]. Thus, a safe, effective, prophylactic HIV vaccine remains one of the priorities of HIV/AIDS research, and will be key to any strategy for halting the AIDS epidemic.

Phase 1 clinical trial HIV-CORE (COnserved REgions) 0052 is a trial of a new combined vaccine regimen to determine safety and immunogenicity in healthy adults in Oxford, UK. Another Trial HIV-CORE 006, using the same vaccine regimen, will be conducted in Eastern and Southern Africa on HIV-1/2-negative individuals. Immune responses may vary between populations and so it is important to confirm that the vaccines are suitable for the people and environment where they will be deployed for protection against HIV/AIDS. There are many different strains of HIV-1, and the virus can change to escape immune responses. This vaccine regimen is designed to work in all parts of the world.

Our aim is to induce effective cytotoxic T-lymphocytes (CTL) against HIV-1. These could complement broadly neutralising antibodies in prophylaxis and play a central role in cure. CTL exert their effector functions by killing HIV-1-infected cells and producing soluble factors, which directly or indirectly counteract the HIV-1 replicative cycle. In future, this approach could be combined, in human efficacy testing, with other vaccines that stimulate humoral responses, with the goal of effectively preventing HIV-1 infections.

The central principle of our strategy is to focus T-cell immune responses on the most conserved regions of the HIV-1 proteome. These regions are common to most variants and, if mutated, reduce the ability of the virus to grow[(5)]; these regions are the “Achilles heel” of HIV-1. Targeting of conserved regions is further enhanced by using ‘mosaic’ proteins, which are designed by computer to maximise

the match of the vaccine with global HIV-1 variants and to block common waysHIV-1 changes to escape the immune response. Vaccines should match circulating HIV-1 variants as much as possible to stop them efficiently. When T-cells attack conserved parts of HIV-1 proteins (parts that seldom or never change), the disease is better controlled—this vaccine employs those parts. The HIV-1-derived mosaic genes are called tHIVconsvX and are delivered by two safe, non-replicating vaccine vectors derived from chimpanzee adenovirus and poxvirus modified vaccinia virus Ankara (MVA). Adenoviruses, if able to grow, normally cause respiratory and gastrointestinal ailments, while the unmodified chimpanzee adenovirus is not known to cause disease in humans; the engineered vaccine vector called ChAdOx1 is crippled so it cannot grow. ChAdOx1 and similar experimental vaccines have been shown to be safe in over 1,500 human volunteers[6–8]. MVA is a poxvirus, which does not replicate in humans. It was used as the smallpox vaccine in over 120,000 people at the end of the smallpox-eradication campaign and as an experimental vaccine vector against a variety of diseases in many clinical trials[9].

Humans and microbiota, which consist of bacteria, fungi, viruses and eukaryotic species, have co-evolved over millions of years and their coexistence is beneficial to both parties. The human immune system is constitutively exposed to microbial stimulation and any vaccine design and responsiveness needs to be considered in the context of host-microbiota interactions. Manipulation of the microbiota functions and composition through diet, engraftment and/or any other means may thus become a viable strategy for improving vaccine responsiveness as well as treating malfunctions of the immune system[10]. The first reports on the influence of gut microbiota diversity and composition on responses to vaccination have been emerging for some time[11–15]. As part of the exploratory endpoints for this trial, we shall characterise the gut microbiome of study volunteers for composition and richness before and after administration of the study vaccines.

In parallel to this trial, HIV-CORE 0052, the same vaccines will be tested in four Clinical Research Centres (CRCs) in Eastern and Southern Africa, in a phase I trial, HIV-CORE 006. The tHIVconsvX vaccines have been designed for global use irrespective of the HIV-1 strain. We do not yet know whether the vaccine will have a beneficial effect, no effect, or whether it could cause harm. The health of trial volunteers will be monitored carefully, and volunteers will receive counselling and support to minimise HIV-1 infection.

3.2. Investigational medicinal products

Rationale for the tHIVconsvX immunogens. The conserved HIV-1 regions of the 2nd generation vaccines used here are in total 872 amino acids (aa) in length and contain only 6 segments of the HIV-1 genome. The global-HIV-1-protein alignments carried out by Los Alamos National Laboratory–HIV Sequence Database (LANL-HSD) *circa* September 2013, were used as the baseline data to define conserved regions. These alignments included only one sequence per individual, and only sequences spanning full-length proteins. Co-optimised, complementary pairs of two mosaic proteins (mosaic 1 and mosaic 2, which differ in 10% aa) were designed[22], 2 regions in Gag and 4 regions in Pol. Conservation was defined by the capacity of the two mosaic proteins to have at least an 9/9-aa match to 80% of the potential 9-aa T-cell epitope (PTE) variants found among the diverse HIV-1 strains in the LANL-HSD alignments. The 80% match to group M HIV-1 isolates cutoff translated into a design of 6 segments from 29 to 333 aa long. Next, both beneficial and detrimental epitopes as defined by Mothe *et al.*[23] were overlaid on vaccine-epitope-coverage maps for the final selection of regions for the 2nd generation conserved vaccine based on all criteria above, and the only regions included were *both* conserved and enriched for beneficial epitopes. Env was deliberately excluded because of high variability and absence of beneficial epitopes. Based on the LANL epitope database, 752 distinct CD8 T-cell epitopes restricted by 84 different HLA class I presenting molecules were contained in the six regions. While these numbers emphasise the rich immunogenic potential of the conserved regions we selected, we fully expect these regions to contain many as yet unknown epitopes[24]. Finally, to avoid boosting with the same irrelevant cross-junctional epitopes, the six regions were arranged in different orders in six tHIVconsvX genes, of which tHIVconsv1, tHIVconsv3 and tHIVconsv5 coded for mosaic 1 and tHIVconsv2, tHIVconsv4 and tHIVcosnv6 coded for mosaic 2. Strong correlations of total tHIVconsvX-specific response magnitude and breadth with low viral load and high CD4 T-cell count were found in a naturally infected treatment naïve population in Japan.

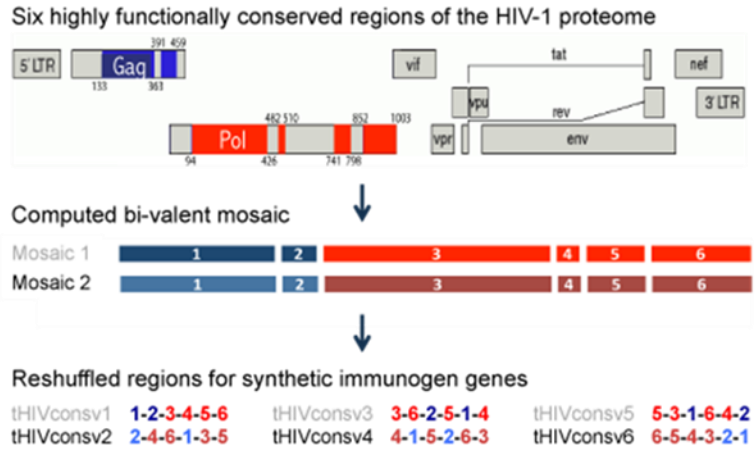


Figure 1. *Six regions of the HIV-1 proteome were selected, which were highly conserved among the group M isolates, and a mutually complementing two sequences of the bi-valent mosaic were computed using curated full protein amino acid sequences present in the LANL-HSD database as of September 2013. Mosaic 1 and mosaic 2 differ in approximately 10% of amino acids, hence two different colours, in order to maximise the match of the vaccines to globally circulating HIV-1 isolates. Synthetic genes were then designed using humanised codons and the 6 regions were organised into 6 different orders to minimise induction of T-cell response to junctional epitopes.*

3.2.1. *The investigational ChAdOx1.tHIVconsv1 vaccine*

The ChAdOx1.tHIVconsv1 vaccine utilises non-replicating engineered simian adenovirus vaccine vector ChAdOx1 derived from simian adenovirus (SAdV) serotype Y25 of chimpanzee origin to deliver a mosaic immunogen tHIVconsv1 derived from functionally conserved regions of HIV-1 proteins.

Rationale for using the ChAdOx1 vaccine vector. Selected types of attenuated adenovirus are very promising as highly immunogenic vaccine vectors[16, 17]. A drawback for the use of the leading human adenovirus serotype 5 (HAdV-5) is pre-existing immunity, mainly neutralising antibodies, found commonly in humans particularly in Africa[16–18]. To circumvent this problem, a number of SAdV serotypes have been explored, which are unaffected by human pre-existing antibodies and display promising T-cell immunogenicity. The genomic DNA of these adenoviruses was cloned into bacterial plasmids, to eliminate any possibility of carrying over adventitious infectious agents from the original hosts. These viruses were rendered replication-incompetent by deletion of the E1 genomic region, their immunogenicity was increased by deletion of the E3 region and their genomes can stably accommodate passenger gene(s). HEK293 cells were used for preparation of high titre GMP virus stocks without the risk of generating contaminating replication-competent adenovirus (RCA) forms.

For the 1st generation vaccines, the attenuated SAdV-derived vaccine vector ChAdV-63 was used. In 2013, GSK acquired Okairos and the ChAdV-63 platform and withdrew further access to this vector. Hence, theswitch to UOXF fully-owned ChAdOx1 was made. Similarly to ChAdV-63, the vaccine vector ChAdOx1 is derived from E-group simian adenovirus, this time from serotype Y25[19], which is at least equally safe and immunogenic to ChAdV-63 in mice[20] non-human primates and humans[21].

3.2.2. *The investigational MVA.tHIVconsv3 and MVA.tHIVconsv4 vaccine components*

Two vaccine components MVA.tHIVconsv3 and MVA.tHIVconsv4 complement each other and will be used as a pair for immunisations. They utilise non-replicating poxvirus MVA delivering bi-valent mosaic immunogens, either tHIVconsv3 or tHIVconsv4, derived from functionally conserved regions of HIV-1 proteins.

Rationale for using MVA as a vaccine vector. Modified vaccinia virus Ankara (MVA) is a vaccinia virus strain, which was attenuated by serial passage in chick embryo fibroblasts (CEF). It has lost 15% of the parental genome, including cytokine receptor genes. It replicates well in CEF and baby hamster cells, but poorly in most mammalian cells[25, 26]. MVA was used as a smallpox vaccine in the early 1970s towards the end of the eradication campaign in 120,000 people, without any serious AEs reported, and is now licensed in the US for use in mass vaccination campaigns (Acambis 2000). Its safety in humans is therefore well established. MVA has been shown to be an effective vaccine vector and induce potent $CD8^+$ T-cell responses to passenger proteins. The immunogenicity of recombinant MVAs has been attributed in part to loss of several cytokine and chemokine receptor genes[27].

The safety and immunogenicity of a range of MVA-vectored vaccine candidates have been demonstrated in the BALB/c and SCID mice and in healthy and SIV-infected rhesus macaques, in GLP toxicology study UNO 0011 and in numerous preclinical studies[28–30]. Similarly, the safety and immunogenicity of a range of MVA-vectored vaccine candidates for HIV-1 and other indications have been demonstrated in a number of clinical studies, in both healthy volunteers and HIV-1-infected volunteers[31–37].

3.3. A summary of findings from non-clinical studies and from other clinical trials

Testing of the 2nd generation conserved region mosaic vaccines is supported by clinical studies of the 1st generation conserved region vaccines and studies of the 2nd generation regions in treatment naïve patients and animal models.

Thus, the 1st generation immunogen HIVconsv used 14 regions designed as clade alternating amino acid consensus (equivalent to a monovalent mosaic)[38]. Vaccines ChAdV63.HIVconsv-MVA.HIVconsv tested in 8 clinical trials, showed promising immunogenicity([32-34, 37, 41-43,44-46] by producing a signal for viremic control in HIV-infected volunteers that were given early ART and 21% patients controlled viremia during monitored ART pause beyond the typical 4 weeks (spontaneous control occurs in 10%-15% patients)[45,46]. Studies in 200 treatment-naïve HIV-1-positive Japanese patients demonstrated a statistically significant correlation between the total magnitude as well as the breadth of the CD8 T-cell responses specific for the conserved regions targeted by the 2nd generation vaccines and low plasma virus load and high CD4 counts[20][39]. All four correlations remained significant for 147 patients who did not have the HLA-B52 and B67 alleles protective in the Japanese population, suggesting that our vaccines could be effective in the entire population rather than only those who have protective HLA class I alleles.

3.3.1 *Pre-clinical experience with the ChAdOx1.tHIVconsv1 vaccine*

ChAdOx1.tHIVconsv1 was safe and immunogenic in BALB/c, C57BL/6J, and CD1-SWISS mice. A formal Good Laboratory Practice (GLP)-compliant acute toxicity study was not deemed necessary, based on data of the first-generation HIV vaccines and other ChAdOx1 vectored vaccines.

First generation vaccines pSG2.HIVconsv DNA, non-replicating simian adenovirus ChAdV63.HIVconsv and poxvirus MVA.HIVconsv, underwent two pre-clinical toxicity studies UNO0011 and UNO0012 at HLS (now Envigo) and were tested in 8 clinical trials in HIV-1-negative and positive individuals in the UK, Spain and Kenya without any concerning safety signals.

Trials with the first-generation HIV vaccines (HIVconsv); DSURs are available on request.

Trial Acronym	n	HIV Status	Site	Registration
HIV-CORE 002	32	Negative	Oxford	NCT0115131
HIV-CORE 003	40	Negative	London	NCT02425241
HIV-CORE 004	72	Negative	Nairobi	NCT02099994
PEACHI-04	32	Negative	Oxford	NCT02362217
HIV-CORE 001	20	Positive	Oxford	NCT01024842
BCN 01	24	Positive	Barcelona	NCT01712425
BCN 02	24	Positive	Barcelona	NCT02616874
RIVER	60	Positive	Multisite UK	NCT02336074

To date, there have been 10 experimental recombinant ChAdOx1 vaccines tested in GLP pre-clinical toxicity studies at ENVIGO and all these uniformly concluded that the intramuscular delivery of the ChAdOx1-vectored vaccines was well tolerated and was not associated with any adverse effects other than those expected from i.m injection and induction of immune responses. For several vaccines, there are safety data already available from humans demonstrating no safety concerns so far.

Toxicity studies on ChAdOx1-vectored experimental vaccines and clinical studies.

Envigo Study No.	Title	Toxicity Report	Trial Registration	EudraCT No.	rChAdOx1 human Dose (vp)
GG05TY	ChAdOx1 LS2 and MVA LS2: Toxicity Study by Intramuscular and Intravenous Administration to Mice	x	NCT03203421	2017-001049-28	5 x 10^9 2.5 x 10^{10}
QS18DL	ChAdOx1 CHIK Vaccine or ChAdOx1 MERS: Toxicity Study by Intramuscular Administration to Mice	x	NCT03399578	2017-003472-31	5 x 10^9 2.5 x 10^{10} 5 x 10^{10}
WC71GC	ChAdOx1 ZIKA and ChAdOx1 CHIK: Toxicity Study by Intramuscular Administration to BALB/c Mice	x	NCT03590392	2017-004483-35	5 x 10^9 2.5 x 10^{10} 5 x 10^{10}
				2019-000075-16	5 x 10^9 2.5 x 10^{10} 5 x 10^{10} 1^10^{11}♠
FP09PP	ChAdOx1 RVF: Toxicity Study by Intramuscular Administration to BALB/c Mice (report in progress)	Report not finalized		2017-004482-27♥	5 x 10^9 2.5 x 10^{10} 5 x 10^{10}
TX05CW	ChAdOx1.HTI: Toxicity Study by Intramuscular Administration to BALB/c Mice	Summary ♣	NCT03204617♦ Added arm		5 x 10^{10}
KH75CL	ChAdOx1 MenB.1: Toxicity Study by Intramuscular Administration to Mice	x	ISRCTN46336916	2017-000965-61	
XMM0003	ChAd OX1 NP+M1 and MVA NP+M1: Toxicity Study by Intramuscular Administration to Mice		NCT01623518	2012-000641-12	2.5 x 10^{10} 5 x 10^{10}
			NCT01818362	2012-004626-25	5 x10^8 5 x10^9 2.5 x10^{10} 5 x10^{10}
XMM0012	ChAdOx1 5T4: Toxicity Study by Intramuscular Administration to Mice	x	NCT02390063	2017-001992-22	2.5 x 10^{10}
			NCT03815942	2017-001992-22	2.5 x 10^{10}
XMM0005	ChAdOx1 85A: Toxicity Study by Intramuscular Administration to Mice		NCT01829490	2012-005118-21	5 x 10^9 2.5 x 10^{10}
			NCT03681860	N/A	2.5 x 10^{10}

♣ *Although constructed by UOXF, the HTI vaccines are being developed by a Spanish SME Aelix Therapeutics. Toxicity reports have been submitted to MHRA under a separate trial, HIV-CORE 0051 and are available on request.*

♦ *Trial Aelix 002 in Spain is currently testing DNA.MVA.HTI in HIV-positive individuals supported by toxicity study LS18WJ. A ChAdOx1.HTI boost will likely be added through amendment.*

♠ *Co-administration of ChAdOx1 ZIKA & ChAdOx1 CHIK*

For the purposes of toxicity, the HIV-1-derived vaccine inserts (immunogens/transgene products), HIVconsv, tHIVconsv1, tHIVconsv3 and tHIVconsv4, employed by experimental vaccines are very similar and indeed, the regions partially overlap among the different immunogen designs. All three HIV immunogen designs (the 1st generation HIVconsv, the 2nd generation tHIVconsvX) are assembled from small regions of HIV-1 proteins, have no biological or enzymatic activity and are joined into a chimeric protein of up to cca 900 amino acids for the sole purpose of inducing CD4 and CD8 T-cell responses. The design of the tHIVconsvX immunogens is depicted in Fig. 1.

Biodistribution studies were not conducted with ChAdOx1.tHIVconsv1. However, previous distribution studies in mice with similar ChAdV-vectored vaccines (AdCh63 ME-TRAP, AdCh63 MSP-1 and AdCh3NSmut) showed no evidence of replication of the virus or presence of disseminated infection after intramuscular (IM) injections. A distribution study was therefore deemed not necessary for ChAdOx1.tHIVconsv1.

3.3.2 *Pre-clinical experience with the MVA.tHIVconsv3 vaccine*

MVA.tHIVconsv3 was demonstrated to be safe, non-toxic and immunogenic in over 1,000 mice during routine experimental immunisations. Formal Good Laboratory Practice (GLP)-compliant acute toxicity and biodistribution studies with MVA.tHIVconsv3 were deemed not necessary based on the cumulative safety data on recombinant MVAs expressing immunogens derived from other pathogens and other immunogens derived from HIV-1 including the very similar first generation conserved-region vaccine MVA.HIVconsv collected by us and, for other recombinant (rMVA), by many other groups around the world over the last four decades.

3.3.3 *Pre-clinical experience with the MVA.tHIVconsv4 vaccine*

MVA.tHIVconsv4 was demonstrated to be safe, non-toxic and immunogenic in over 1,000 BALB/c, C57BL and CD1-SWISS mice during routine experimental immunisations. A formal GLP-compliant acute toxicity study with MVA.tHIVconsv4 was deemed not necessary based on the vast cumulative safety data on recombinant MVAs expressing immunogens derived from other pathogens and other immunogens derived from HIV-1 including the very similar first generation conserved-region vaccine MVA.HIVconsv collected by us and, for other rMVAs, by many other groups around the world over the last four decades.

3.3.4 *Clinical experience with MVA.tHIVconsv3 and MVA.tHIVconsv4*

M&M Clinical Trial (NCT03844386) is the first-in-human clinical trial using MVA.tHIVconsv3 and MVA.tHIVconsv4. This is a double blind, randomized, placebo-controlled, parallel design, study in which 24 HIV-infected participants with durable viral suppression will be randomly assigned to receive vaccination with MVA.tHIVconsv3 (M3), MVA.tHIVconsv4 (M4), M3+M4 combined, or placebo. To date, 5 individuals were enrolled; no SAEs were recorded. A non-remarkable safety profile is expected based on numerous previous and ongoing clinical trials using MVA as a viral vaccine vector.

3.3.5 *General investigational plan of the vaccines used in the trial*

The clinical assessment of the vaccines used in this trial is aimed towards the evaluation of their safety, immunogenicity and efficacy as a part of a multicomponent experimental vaccination regimen developed for prevention and treatment of HIV-1 infection. The full vaccination regimen will encompass priming with non-replicating recombinant simian (chimpanzee) adenoviruses ChAdOx1.tHIVconsv1 + ChAdOx1.HIVconsv62 and boosting with MVA.tHIVconsv3 + MVA.tHIVconsv4. Env component(s) might be added in the future for induction of broadly neutralising antibodies.

For prophylaxis in HIV-1-negative subjects, trial HIV-CORE 0052 will be the first-in-man study in UK healthy adult volunteers. Data derived from HIV-CORE 0052 will provide the ground to design similar studies in different populations. A multi-centre phase 1 trial (HIV-CORE 006) is under preparation with the aim of establishing safety and immunogenicity of the second generation tHIVconsvX vaccines in the ultimate target populations in Kenya, Uganda and Zambia. Other trials in Italy, the US and South Africa will test the safety, immunogenicity and efficacy of similar multicomponent regimens in HIV-1-positive subjects receiving antiretroviral treatment.

3.4 Conducting the trial in the context of the COVID-19 pandemic

To minimise potential risk, clinical activity will be conducted in line with the latest Public Health England (PHE) advice. Local SOPs for the use of appropriate personal protective equipment (PPE) and social distancing will be followed by clinical staff.

Volunteers will receive a generic COVID-19 restrictions information sheet detailing the arrangements that are taking place to allow the trial to continue safely.

They will agree to adhere to PHE advice regarding symptoms and isolation, social distancing and COVID-19 testing (if necessary) while participating in the trial. COVID-19 testing during the trial will be applicable as per PHE guidance and according to symptoms or contacts.

During the COVID-19 pandemic, when government advice prevents non-essential study visits and to limit the risk of unnecessary exposure to COVID-19 enrolment to this trial may be paused, with no screening or vaccination/enrolment visits conducted.

For participants enrolled prior to such governmental advice or between periods of such advice, all scheduled visits may be conducted remotely (via telephone) and the participant will only be asked to attend the clinic if there are any safety concerns. Safety and immunology bloods will be taken at the earliest convenience in an unscheduled visit at discretion of the investigator.

If a volunteer is self-isolating at the time of a scheduled follow-up appointment, they will be assessed via telephone and the appointment will be re-scheduled using the time windows if possible. If this is not possible, all relevant data that can be collected by phone will be recorded in the corresponding eCRF. Safety and immunology bloods will be taken at the earliest convenience in an unscheduled visit at discretion of the investigator.

During the COVID-19 epidemic in the UK, volunteers and their household members will be advised on whether they require to self-isolate according to PHE guidance on vaccinations. No self-isolation is required when fever is an expected vaccination reaction, unless COVID-19 is suspected (e.g. if other symptoms associated with COVID-19 co-exist). Fever which usually resolves within 48 hours is a systemic expected adverse reaction from vaccination with ChAdOx1.tHIVconsv1, MVA.tHIVconsv3 and MVA.tHIVconsv4. If the volunteer is persistently febrile, has other COVID-19 symptoms, or the clinical investigator considers it necessary, the volunteer will be advised to follow PHE guidance on self-isolation and testing.

4. OBJECTIVES AND OUTCOME MEASURES

The purpose of this trial is to determine whether the vaccination regimen is safe, tolerable and immunogenic. The vaccine immunogens tHIVconsvX were designed for maximum match with group M global HIV-1 isolates. This study will test the specificity, magnitude and functionality of T-cell responses after a regimen of one dose of ChAdOx1.tHIVconsv1 prime followed by MVA.tHIVconsv3 and MVA.tHIVconsv4 as a boost.

Objectives	Endpoints/Outcome Measures	Timepoint(s) of evaluation of this outcome measure (if applicable)
Primary Objectives • To evaluate the safety and tolerability of ChAdOx1.tHIVconsv1 given alone and in a prime boost vaccine regimen followed by MVA.tHIVconsv3 and MVA.tHIVconsv4	• Proportion of volunteers who experience local and systemic reactogenicity events • Proportion of volunteers with Grade 3 or 4 unsolicited AEs • Proportion of volunteers with vaccine related SAEs	• Within 7 days post vaccination • Through 28 days post final vaccination • Throughout the study period
Secondary Objectives To determine: • the proportion of vaccine recipients who develop tHIVconsvX specific T-cell responses induced by the ChAdOx1.tHIVconsv1 followed by MVA.tHIVconsv3 & 4 vaccines	• Proportion of vaccine recipients developing HIV-1 specific T-cell responses	• At 1 and 20 weeks post final vaccination
To assess: • the tHIVconsvX-specific T-cell responses for their frequency, breadth and duration in vaccine responders	• Frequency, breadth and duration of the tHIVconsvX-specific T-cell responses to conserved epitopes measured in the IFN-γ ELISpot assay in each vaccine recipient	• At 1 and 20 weeks post final vaccination

Objectives	Endpoints/Outcome Measures	Timepoint(s) of evaluation of this outcome measure (if applicable)
• Ability of the tHIVconsvX-specific T-cell responses to inhibit replication *in vitro* of viruses of four major HIV-1 clades A, B, C and D	• Breadth of inhibition of HIV-1 viruses	• At 1 and 20 weeks post final vaccination
Exploratory Objectives		
• To assess the plurifunctionality of the tHIVconsvX-specific T-cells in the vaccine responders	• Proportions of mono-, bi- and tri-functional tHIVconsvX specific T-cells in the vaccine recipients	• At 1 and 20 weeks post final vaccination
• To characterise the gut microbiome composition and richness	• Shotgun sequencing and metabolomics analyses	• Before vaccination, at 1 and 20 weeks post final vaccination

5. TRIAL DESIGN

This is an open-label, dose escalation phase 1 clinical trial to assess the safety and immunogenicity of the candidate vaccines ChAdOx1.tHIVconsv1, MVA.tHIVcons3 and MVA.tHIVconsv4 in a prime boost regimen in healthy HIV-1/2-negative volunteers aged 18-65. The vaccines will be administered intramuscularly, in the deltoid region of each arm.

5.1 Rationale for selected doses

The total doses employed as well as the heterologous-prime-boost chimp adenovirus-MVA regimen have been tested and optimised for these types of vaccine vectors in many human volunteers for HIV-1 and other disease candidate vaccines.

A first-in-human dose escalation study using the ChAdOx1 vector encoding an influenza antigen (FLU004), safely administered ChAdOx1 NP+M1 at doses ranging from 5×10^8 to 5×10^{10} vp. In two clinical studies conducted in Oxford (CHIK001 and MERS001), ChAdOx1 vector was administered at the dose 5×10^{10} vp to 18 healthy volunteers, with no safety concerns. ChAdOx1 vectored vaccines have thus far been demonstrated to be very well tolerated. The vast majority of AEs have been mild-moderate and there have been no SARs reported to date.

ChAdOx1.tHIVconsv1 (C1) has not been tested on humans before, and the first three participants will receive a low dose of the vaccine (group 1). After safety review, the next 10 volunteers (group 2) will receive a higher dose of C1, followed by MVA.tHIVconsv3 & 4 (M3M4). The 4-week interval was shown to be equivalent to the 8-week interval in the HIV-CORE 003 trial and studies with Ebola vaccines (AVS Hill, UOXF; personal communication).

The optimal dose of rMVAs were shown consistently to be 1-2 x 10^8 pfu. Higher doses of rMVAs (2.5-5 x 10^8 pfu) were associated with marked reactogenicity, with severe 'flu-like' systemic AEs recorded in a previous study in Oxford. Lower doses of rMVAs enable an acceptable reactogenicity profile without significantly compromising vaccine immunogenicity.

Clinical studies have shown IM administration to be associated with fewer and short-lived local AEs and no reduction in immunogenicity[40].

5.2 Study groups

Volunteers will be recruited and vaccinated at the CCVTM, Oxford. There will be 2 study groups and a total of 13 volunteers will be enrolled (Table 1).

Table 1. Study groups.

Group	Vaccines	Dose
Group 1 (n=3)	ChAdOx1.tHIVconsv1 (C1)	5 x 10^9 vp
Group 2 (n=10)	ChadOx1.tHIVconsv1 (C1) MVA.tHIVconsv3 (M3) MVA.tHIVconsv4 (M4)	5 x 10^{10} vp 1 x 10^8 pfu 0.9 x 10^8 pfu

5.2.1 *Group Enrolment*

As this is a first-in-man trial of the ChAdOx1.tHIVconsv1, volunteers will be recruited in a step-wise fashion as follows:

Group 1: The first volunteer in the study will receive 5 x10^9 vp of ChAdOx1.tHIVconsv1. This volunteer will be vaccinated ahead of any other volunteers and the profile of AEs will be examined after 48 hours (+24 hours). Provided there are no safety concerns as assessed by the Chief Investigator (CI) and the Local Safety Monitor (LSM), another 2 volunteers will be vaccinated at the same dose after at least 48 hours has elapsed following vaccination of the first volunteer and at least 1 hour apart from each other.

Group 2: An independent safety review will be conducted by the LSM after vaccination of the 3 volunteers in group 1. This review will include the results of safety blood tests at day 7 post vaccination and an assessment of the profile of the AEs reported. The CI and the LSM will be asked to provide the decision on whether to proceed with vaccination of the first volunteer to receive 5 x10^{10} vp of ChAdOx1.tHIVconsv1. If, following safety review by the CI and LSM, there are no safety concerns at 48 hours (+24 hours) post-vaccination of the first volunteer in group 2, a further two group 2 volunteers may receive vaccination with ChAdOx1.tHIVconsv1 high dose and at least 1 hour apart from each other. If there are no safety concerns following review by the CI and LSM of these volunteers at seven days post-vaccination, the remaining group 2 volunteers may receive vaccination. The same staggered enrolment will be followed for MVA.tHIVconsv3&4. No escalation dose will be required for this vaccines, as they have been administered to humans before.

5.3 Trial volunteers

As far as possible, equal numbers of adult men and women will be recruited to this study and members of different racial and ethnic groups enrolled commensurate with their representation in the population. Subjects will be low-risk, HIV-1/2-uninfected adult volunteers aged 18-65 who fully comprehend the purpose and details of this study as provided in the Participant Information Sheet and are able to provide informed consent. Eligibility will depend on the results of laboratory tests, review of medical history, physical exam results and answers to questions about risk behaviours.

Date of enrolment is the date of first vaccination.

5.4 Duration of study

The total duration of the study will be 4 months and 5 months from the day of enrolment, for group 1 and group 2, respectively.

5.5 Definition of start and end of trial

The start of the trial is defined as the date the first volunteer is recruited to the trial (i.e. the date the first volunteer provides informed consent). The end of the trial is the date of the last visit of the last volunteer.

5.6 Potential risks for volunteers

The potential risks are those associated with phlebotomy and vaccination.

- ***Venepuncture and intravenous cannulation***

The total volume of blood drawn per visit and over the four or five-month study period (less than 100ml for Group1 participants or less than 600ml for Group 2 participants) is not expected to compromise volunteers' health. This is less than the volume allowed for both male and female blood donors over a similar period, therefore we do not anticipate AEs as a consequence of blood sampling. We will monitor for anaemia at regular intervals, as indicated in the Schedule of Procedures and participants will be asked to refrain from blood donation for the duration of their involvement in the trial.

Mild tenderness, bruising at the site of needle insertion, light-headedness, or rarely, syncope, may result from venepuncture. Study participants will be seated or reclining in order to minimise the risk of the latter.

- ***Allergic reactions***

Allergic reactions from mild to severe may occur in response to any constituent of a medicinal product's preparation. Anaphylaxis is extremely rare (less than 1 in 1,000 people) but can occur in response to any vaccine or medication. Advanced Life Support trained physicians, equipment and drugs are immediately available for the management of any serious adverse reactions (SAR).

- ***Vaccination***

Local reaction from IM vaccination

Typical local reactions as a result of IM injections are temporary pain, redness and swelling at the site of the injection.

Systemic reactions

Constitutional influenza-like symptoms such as fatigue, headache, malaise, feverishness, joint and muscle aches can occur with any vaccination and last for 2-3 days. As with any other vaccine, temporary ascending paralysis (Guillain-Barré syndrome (GBS)) or immune mediated reactions that can lead to organ damage may occur, but these are extremely rare. For influenza vaccines an excess of approximately 1 GBS case per million persons immunised has been observed. No cases were observed in people under 45 years of age. Neither wild-type human adenoviruses nor vaccinia infections were associated with an increased risk of GBS, therefore, the possibility of this occurring as a result of vaccination with replication-defective viral vectors is extremely remote. Systemic reactogenicity of the vaccines is one of the primary safety and tolerability endpoints of the study and will be assessed by self-reported symptoms and clinical examination.

Very rare potential side effects described with similar vaccines

The ChAdOx1 part of the vaccine (the "viral vector" or "backbone") is the same as has been used in a recently developed COVID-19 vaccine (ChAdOx1 nCoV-19 - commonly known as the Oxford/AstraZeneca vaccine or Vaxzevria). In the Spring of 2021, some countries that were using this vaccine for their national COVID-19 immunisation programmes temporarily paused the use of the

vaccine due to concerns that rare blood clotting conditions could be associated with the vaccine. Following these reports, a review has been undertaken by the MHRA (Medicines and Healthcare products Regulatory Agency) and the EMA (European Medicines Agency). The reports were of a very rare type of blood clot in the brain, known as cerebral venous sinus thrombosis (CVST), and also of clots in some other organs together, with low levels of platelets (thrombocytopenia). Up to and including 31 March 2021 there have been 79 UK reports of these blood clots and unfortunately 19 people died. By 31 March 2021 20.2 million doses of the ChAdOx1 nCoV-19 vaccine had been given in the UK. This means the overall risk of these blood clots is extremely rare, approximately 4 people in a million who receive the vaccine.

After investigation, the UK Medicines Healthcare Regulatory Agency concluded, based on the data currently available to them, they could not say that there was a definite link between the vaccine and the rare clotting events.

The European Medicines Agency concluded that unusual blood clots with low blood platelets should be listed as very rare side effects of this vaccine.

Both agencies concluded that there wasn't enough evidence at present to say what the risk factors (e.g. age, gender, or other medical conditions) might be for having one of these rare clotting problems.

HIV-1 Testing

Only volunteers who are HIV-1 seronegative at screening will participate in the study. The HIV screening tests and routine post-vaccination tests will be performed as specified in the Schedule of Procedures (Table 2).

If a volunteer during or after the study is found to be HIV-1-seropositive, a newly drawn blood specimen will be collected for confirmation.

It is extremely unlikely that the study vaccines induce antibodies against HIV-1, as these vaccines are designed to elicit T-cell responses. However, if a volunteer appears to have developed HIV-1-specific antibodies as a result of vaccination and these cause reactivity on a standard HIV ELISA test, they will be given a letter clearly stating that HIV antibodies developed as a result of vaccination and not as a result of HIV infection. A copy of this letter will also be sent to the volunteer's General Practitioner (GP).

If a participant suspects they have been exposed to HIV during the study, they would be recommended to contact the trial nurse/physician first. A risk assessment would be carried out by the trial nurse/physician and the volunteer would be offered an HIV-1 antibody test at the trial site, or referred to a GUM or ID clinic if s/he prefers this option. Written information concerning tests performed and results will be provided upon request.

Volunteers who are found to be HIV-1-seropositive at screening and volunteers who acquire HIV-1 infection during the study will receive counselling and referral for support and/or care.

- ***Potential interaction with other adenoviral vectored vaccines***

The 'vector' (ChAdOx1) used in the ChAdOx1.tHIVconsv1 experimental vaccine is the same as the one used in the Oxford AstraZeneca and similar to the one used in the Janssen (Johnson and Johnson) Covid-19 vaccines (Adenovirus 26). There is a theoretical risk that receiving the experimental ChAdOX1.tHIVconsv1 vaccine may reduce the benefit of subsequent administrations of certain vaccines such as the Janssen (Johnson & Johnson) or the AstraZeneca Covid-19 vaccines. This may be more likely to happen if the vaccines are given at short intervals. The immune response to the AstraZeneca Covid-19 vaccine was not affected in those who received another experimental ChAdOx1 vectored vaccine one year earlier[47,48] . Other studies suggest that an interval of three months between administrations of two adenoviral vectored vaccines reduces the risk of this interference[49-53]. For this reason, we will enrol participants who have been vaccinated with an mRNA Covid vaccine or will have their NHS Covid vaccine offer at least three months after the ChAdOx1.tHIVconsv. No such interference will be expected with mRNA or protein vaccines (such as Moderna, Pfizer, Novavax) and these can be given at least 2 weeks before or after the ChAdOx1.tHIVconsv1 dose.

5.7 Known potential benefits

Volunteers will not benefit directly from participation in this study. However, it is hoped that the information gained from this study will contribute to the development of a safe and effective HIV-1 vaccine regime. The only benefits for participants would be information about their general health status, HIV and Sexually Transmitted Infections (STI) counselling and testing.

6. RECRUITMENT AND WITHDRAWAL OF TRIAL VOLUNTEERS

6.1 Identification of trial volunteers

Healthy, low-risk, HIV-1/2-negative adults will be recruited by use of an advertisement +/- registration form formally approved by the ethics committee(s) and distributed or posted in the following places:

- In public places, including buses and trains, with the agreement of the owner/proprietor.
- In newspapers or other literature for circulation.
- Via radio announcements.
- On a website or social media site operated by our group or with the agreement of the owner or operator (including on-line recruitment through our web-site).
- By e-mail distribution to a group or list only with the express agreement of the network administrator or with equivalent authorisation.
- By email distribution to individuals who have already expressed an interest in taking part in any clinical trial at the Oxford Vaccine Centre.
- On stalls or stands at exhibitions or fairs.
- Via presentations (e.g. presentations at lectures or invited seminars).
- Direct mail-out: This will involve obtaining names and addresses of adults via the most recent Electoral Roll. The contact details of individuals who have indicated that they do not wish to receive postal mail-shots would be removed prior to the investigators being given this information. The company providing this service is registered under the relevant data protection legislation. Investigators would not be given dates of birth or ages of individuals but the list supplied would only contain names of those aged between 18 and 65 years (as per the inclusion criteria).

  Oxford Vaccine Centre databases: We may contact individuals from databases of groups within the CCVTM (including the Oxford Vaccine Centre database) of previous trial participants who have expressed an interest in receiving information about all future studies for which they may be eligible.

6.2 Informed consent

All volunteers will sign and date the informed consent form before any study specific procedures are performed. The information sheet will be made available to the volunteer at least 24 hours prior to the screening visit. At the screening visit, the volunteer will be fully informed of all aspects of the trial, the potential risks and their obligations. The following general principles will be emphasised:

- Participation in the study is entirely voluntary
- Refusal to participate involves no penalty or loss of medical benefits
- The volunteer may withdraw from the study at any time
- The volunteer is free to ask questions at any time to allow him or her to understand the purpose of the study and the procedures involved
- The study involves research of an investigational vaccine
- There is no direct benefit to the volunteer from participating
- The volunteer's GP will be contacted to corroborate their medical history
- With their consent, the volunteer's blood and faecal samples taken as part of the study will be stored indefinitely in the ethically approved OVC Biobank. Samples may be sent outside of the UK and Europe to laboratories in collaboration with the University of Oxford. These will be anonymised.

The aims of the study and all tests to be carried out will be explained. The volunteer will be given the opportunity to ask about details of the trial, and will then have time to consider whether or not to participate. If they do decide to participate, they will sign and date the consent form. The Investigator will also sign and date the form. A copy will be made for the volunteer to take away and keep, and the original will be stored in the case report form (CRF) – this is a paper or electronic document used to collect data relating to a particular volunteer.

6.3 Inclusion and exclusion criteria

This study will be conducted in healthy adults, who meet the following inclusion and exclusion criteria.

6.3.1 *Inclusion criteria*

The volunteer must satisfy all the following criteria to be eligible for the study:

- Healthy adult aged 18-65 years
- Able and willing (in the Investigator's opinion) to comply with all study requirements
- Willing to allow the investigators to discuss the volunteer's medical history with their GP
- Women of child-bearing potential agree to practice continuous effective contraception (see below) during the study and test negative for pregnancy on the day(s) of screening and vaccination
- For sexually active men, willingness to use barrier methods for the purposes of contraception from screening until 4 months after the last vaccination
- Agreement to refrain from blood donation during the course of the study
- In the opinion of the Investigators, the volunteer has understood the information provided Written informed consent must be given before any study-related procedures are performed
- Willing to undergo HCV, HBV, syphilis and HIV testing and counselling and receive test results

6.3.2 *Exclusion criteria*

The volunteer may not enter the study if any of the following apply:

- Confirmed HIV-1 or HIV-2 infection
- Participation in another research study involving receipt of an investigational product in the 30 days preceding enrolment, or planned use during the study period
- Receipt of a recombinant simian adenoviral vaccine prior to enrolment
- Planned receipt of another adenoviral vectored vaccine within 90 days after the vaccination with the ChAdOx1.tHIVconsv1 IMP
- Receipt of any investigational HIV-1/2 vaccine
- Receipt of live attenuated vaccine within the previous 60 days or planned receipt within 60 days after vaccination with the IMP
- Receipt of other vaccine, including influenza vaccine, within the previous 14 days or planned receipt within 14 days after vaccination with the IMP
- Administration of immunoglobulins and/or any blood products within the three months preceding the planned administration of the vaccine candidate

- Any confirmed or suspected immunosuppressive or immunodeficient state, including HIV-1/2 infection; asplenia; recurrent, severe infections and chronic (more than 14 days) immunosuppressant medication within the past 6 months (inhaled and topical steroids are allowed)
- History of allergic disease or reactions likely to be exacerbated by any component of the vaccine
- Any history of hereditary angioedema, acquired angioedema, or idiopathic angioedema.
- Any history of anaphylaxis in relation to vaccination
- Pregnancy, lactation or willingness/intention to become pregnant during the study
- History of cancer (except basal cell carcinoma of the skin)
- History of serious psychiatric condition likely to affect participation in the study
- Bleeding disorder (eg. Factor deficiency, coagulopathy or platelet disorder), or prior history of significant bleeding or bruising following IM injections or venepuncture
- Any other serious chronic illness requiring hospital specialist supervision
- Suspected or known current alcohol abuse as defined by an alcohol intake of greater than 42 units every week
- Suspected or known injecting drug abuse in the 5 years preceding enrolment
- Reported high-risk behaviour for HIV-1/2 infection. High-risk behaviour for HIV-1/2 infection is defined as follows. Within the previous 12 months the volunteer has:
    - Had unprotected vaginal or anal sex with a person infected with HIV and not taking effective treatment, injecting drug users or casual partners (i.e., no continuing, established relationship)
    - Engaged in sex work for money or drugs
    - Used injection drugs
    - Acquired one of the following sexually transmitted infection: chlamydia, gonorrhea and syphilis.
- Seropositive for hepatitis B surface antigen (HBsAg)
- Seropositive for hepatitis C virus (antibodies to HCV)
- Untreated Syphilis: Treponemal IgG/IgM and positive RPR/TPPA AND no documentation of adequate treatment

- Any other significant disease, disorder or finding which may significantly increase the risk to the volunteer because of participation in the study, affect the ability of the volunteer to participate in the study or impair interpretation of the study data

6.3.3 *Effective contraception for female volunteers*

Female volunteers are required to use an effective form of contraception during the course of the study. Acceptable forms of contraception for female volunteers include:

- Established use of oral, injected or implanted hormonal methods of contraception.
- Placement of an intrauterine device (IUD) or intrauterine system (IUS).
- Total abdominal hysterectomy
- Male sterilisation, if the vasectomised partner is the sole partner for the subject.
- True abstinence, when this is in line with the preferred and usual lifestyle of the subject (Periodic abstinence and withdrawal are not acceptable methods of contraception)

Barrier methods for the purposes of contraception (condom or occlusive cap with spermicide) for female volunteers are not acceptable as they are not considered “highly effective” (i.e. <1% failure rate).

6.3.4 *Temporary Exclusion Criteria*

The following AEs constitute contraindications to administration of vaccine at that point in time; if any one of these AEs occur at the time scheduled for vaccination, the subject may be vaccinated at a later date, or withdrawn at the discretion of the CI. The subject must be followed until resolution of the event as with any AE:

- Acute disease at the time of vaccination. (Acute disease is defined as the presence of a moderate or severe illness with or without fever). Most vaccines can be administered to persons with a minor illness such as diarrhoea, mild upper respiratory infection with no fever or low-grade febrile illness (i.e. temperature of ≤37.5 °C/99.5 °F) at the discretion of the reviewing clinician. The decision to proceed with vaccination in this situation should be clearly explained in the CRF with careful consideration given to causality assignment of AEs which occur during the post vaccination period.
- Temperature of >37.5 °C (99.5 °F) at the time of vaccination.

6.3.5 *Prevention of 'Over Volunteering'*

Volunteers will be excluded from the study if they are concurrently involved in another trial. In order to ensure this, volunteers will be asked to provide their National Insurance or Passport number (if they are not entitled to a NI number) and will be registered on a national database of participants in clinical trials (*www.tops.org.uk*). They will not be enrolled if found to be actively registered on another trial.

6.3.6 *Withdrawal of Volunteers*

In accordance with the principles of the current revision of the Declaration of Helsinki and any other applicable regulations, a volunteer has the right to withdraw from the study at any time and for any reason, and is not obliged to give his or her reasons for doing so. The Investigator may withdraw the volunteer at any time in the interests of the volunteer's health and well-being. In addition, the volunteer may be withdrawn by the investigator for any of the following reasons:

- Administrative decision by the Investigator.
- Ineligibility (either arising during the study or retrospectively, having been overlooked at screening).
- Significant protocol deviation.
- Volunteer non-compliance with study requirements.
- An AE, which requires discontinuation of the study involvement or results in inability to continue to comply with study procedures.

The reason for withdrawal will be recorded in the CRF. If withdrawal is due to an AE, appropriate follow-up visits or medical care will be arranged, with the agreement of the volunteer, until the AE has resolved, stabilised or a non-trial related causality has been assigned. Any volunteer who is withdrawn from the study may be replaced, if that is possible within the specified time frame. The Local Safety Monitor (LSM) may recommend withdrawal of volunteers; however, the final decision will be made by the CI. Any volunteer who fails to attend for two or more follow-up visits during the study, despite active attempts to contact volunteer by trial team, will be deemed to have withdrawn from the study.

If a volunteer withdraws from the study, blood samples collected before their withdrawal from the trial will be used/ stored unless the volunteer specifically requests otherwise.

Participants who receive another adenoviral vectored vaccine as part of the national Covid-19 immunisation programme within 3 months from ChAdOx1.tHIVconsv1 will remain in the study, but data might be analysed separately from the rest of the cohort.

6.4 Compliance with dosing regime

All vaccinations will be administered by the Investigator and recorded in the CRF. The study IMP will be at no time in the possession of the volunteer and compliance will not, therefore, be an issue.

6.5 Pregnancy

Should a volunteer become pregnant during the trial, no further study IMP will be administered. The volunteer will be followed up for clinical safety assessment with their ongoing consent and in addition will be followed until pregnancy outcome is determined. We would not routinely perform venepuncture in a pregnant volunteer unless there is clinical need.

7. CLINICAL PROCEDURES

This section describes the clinical procedures for evaluating study participants and follow-up after administration of study vaccine.

7.1 Schedule of Attendance

All volunteers will have the schedule of clinic attendances and procedures as indicated in the schedules of attendance (Table 2). The total volume of blood to be taken at each visit will vary and can be up to approximately 130 ml. Additional visits or procedures may be performed at the discretion of the investigators, e.g., further medical history and physical examination, blood tests in event of laboratory abnormalities leading to AE, or urine microscopy in the event of positive urinalysis.

2. Schedule of Procedure

2a. Schedule of Procedures of group 1

Visit number	**Screen**	**1**	**2**	**3**	**4**	**5**	**6**
Study week	**Screen**	**0**	**1**	**1**	**2**	**4**	**16**
Study day	**-42**	**0**	**1**	**7**	**14**[1]	**28**	**112**[2]
Visit windows (days)	(≤ -42)	0	-	±3	±3	±3	±7
Informed consent	X						
Confirm eligibility	X	X					
VACCINATION							
ChAdOx1.tHIVconsv1 low dose		X					
COUNSELLING							
HIV Risk Reduction Counselling	X	X					X
HIV Test Counselling	X	X					X
CLINICAL ASSESSMENTS							
HIV-1 Risk Assessment	X						
Comprehensive Medical History	X						
Interim Medical History		X	X	X	X	X	X
General Physical Exam	X	X					
Symptom Directed Physical Exam			X	X		X	X
Weight	X						
Height	X						
Vital signs	X	X[3]	X	X		X	X
Cervical & Axillary lymph nodes		X	X	X			
Adverse Events		X	X	X	X	X	X
Serious Adverse Events		X	X	X	X	X	X
Concomitant Medications	X	X	X	X	X	X	X
Local and Systemic Reactogenicity Assessment[1]		X[4]		X			
LABORATORY PROCEDURES							
HBsAg, HCV Antibodies (5 ml)	X						X
Syphilis serology	X						X
HIV-Ab (5 ml- when HBsAG and HCV Ab are required, no additional blood for HIV-Ab is needed)	X	X					X
HIV-RNA (10 ml)							X
Urinalysis	X						
Routine Haematology (2 ml)	X	X	X	X		X	X
Coagulation screen and fibrinogen (3 ml)	X	X				X	
Biochemistry (4 ml)	X	X		X		X	
Pregnancy Test (if applicable)	X	X					X
Blood volume per visit (ml)	21	13	2	6		9	17
Cumulative blood volume (ml)		34	36	42		51	68

[1] *Visit D14 will be conducted by phone; participants might need to attend the clinic at discretion of the investigator. If participants attend the clinic, the visit will be recorded as unscheduled visit.*

[2]*Early Termination (ET): Procedures to be performed at ET are the same as the week 16 visit procedures.*

[3]*Collect at baseline and at 30 (±5 min) min post vaccination; first participant in each group will have additional observation at 60 min (±5 min)*

[4]*Reactogenicity will be collected from Day 0 to Day 7 after each vaccination.*

Table 2b. Schedule of procedures of Group 2

Visit number	**Screen**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**
Study Week	**Screen**	**0**	**1**	**1**	**2**	**4**	**4**	**5**	**6**	**8**	**9**	**20**[2]
Study day	**-42**	**0**	**1**	**7**	**14**[1]	**28**	**29**	**35**	**42**	**56**	**84**	**140**
Visit windows (days)	(≤ -42)	0	0	±3	±3	±3	0	±3	±3	±3	±7	±7
Informed consent	X											
Confirm eligibility	X	X										
VACCINATIONS												
ChAdOx1.tHIVconsv1 high dose		X										
MVA.tHIVconsv3 and MVA.tHIVconsv4						X						
COUNSELLING												
HIV Test Counselling	X	X				X						X
CLINICAL ASSESSMENTS												
HIV-1 Risk Assessment	X											
Comprehensive Medical History	X											
Interim Medical History		X	X	X	X	X	X	X	X	X	X	X
General Physical Exam	X	X				X						
Symptom Directed Physical Exam			X	X			X	X	X	X	X	X
Weight	X											
Height	X											
Vital signs	X	X[3]	X	X		X[3]	X	X	X	X	X	X
Cervical & Axillary lymph nodes		X	X	X		X	X	X				
Adverse Events		X	X	X	X	X	X	X	X	X		
Serious Adverse Events		X	X	X	X	X	X	X	X	X	X	X
Concomitant Medications	X	X	X	X	X	X	X	X	X	X		
Local and Systemic Reactogenicity Assessment[1]		X[4]	X	X		X[4]	X	X				
LABORATORY PROCEDURES												
HBsAg, HCV Ab (5 ml)	X											X
Syphilis serology	X											X
HIV-Ab (5 ml- when HBsAG and HCV Ab are required, no additional blood for HIV-Ab is needed)	X	X				X						X
HIV-RNA (10 ml)												X
Urinalysis	X											
Routine Haematology (2 ml)	X	X	X	X		X	X	X		X		X
Coagulation screen and fibrinogen(3 ml)	X	X				X				X		
Biochemistry (4 ml)	X	X		X		X		X		X		
Pregnancy Test (if applicable)	X	X				X						X
Faecal samples		X[5]						X				X
IMMUNOLOGY												
HLA Typing (4 ml)		X										
Fresh ELISpots (20 ml)		X						X				X
PBMC, serum and plasma storage (frozen ELISpot, VIA, ICS, memory) (100 ml)		X						X	X			X
Epitope Mapping (20 ml)										X	X	
Innate response (2.5 ml)		2.5	2.5	2.5		2.5	2.5	2.5			2.5	2.5
Blood volume per visit (ml)	14	140.5	4.5	8.5	-	16.5	4.5	128.5	100	20	22.5	139.5
Cumulative blood volume (ml)	14	154.5	159	167.5	167.5	184	188.5	317	417	437	459.5	599

[1] Visit D14 will be conducted by phone; participants might need to attend the clinic at discretion of the investigator. If participants attend the clinic, the visit will be recorded as unscheduled visit.
[2]Early Termination (ET): Procedures to be performed at ET are the same as the week 20 visit procedures.
[3] Collect at baseline and at 30 (±5 min) min post vaccination; first participant in each group will have additional observation at 60 min (±5 min)
[4]Reactogenicity will be collected from Day 0 to Day 7 after each vaccination.
[5] Faecal sample should be collected before administration of the first vaccine dose at enrolment

7.2 Observations

Pulse, blood pressure and temperature will be measured at the time-points indicated in the schedule of procedures and may also be measured as part of a physical examination if indicated at other time-points.

7.3 Blood tests and urinalysis

Blood will be drawn for the following laboratory tests and processed at Oxford University Hospitals NHS Foundation Trust using NHS standard procedures:

- **Haematology;** Full Blood Count – 2 ml taken at screening visit, at each vaccination visit and at 1, 7 and 28 days post each vaccination visit
- **Biochemistry;** Sodium, Potassium, Urea, Creatinine, Albumin, Liver Function Tests (ALT, ALP, bilirubin) – 4 ml taken at screening visit, at each vaccination visit, 7 and 28 days post each vaccination visit
- **Coagulation screen and fibrinogen:** Prothrombin time, APTT and fibrinogen – 3 ml taken at screening visit, each vaccination visit and 28 days post each vaccination visit
- **Diagnostic serology:** HBsAg, HCV antibodies, HIV antibodies, Treponemal IgG/IgM ±RPR– 5 ml taken at screening visit and at the final visit. Other 5 ml samples for HIV antibodies only are taken at each vaccination visit and the final visit
- **HIV-RNA**: this test will be done at the final visit
- **Urinalysis**: Urine will be tested for protein, blood and glucose at screening using a dipstick. . For female volunteers only, urine will be tested for beta-human chorionic gonadotrophin (β-HCG) at screening, immediately prior to vaccination and at the final visit

Additional safety blood tests may be performed if clinically relevant at the discretion of the medically qualified investigators.

At University of Oxford research laboratories (Group 2 only):

- **Exploratory Immunology**; Immunogenicity will be assessed by a variety of immunological assays. This includes T-cell assays including *ex vivo* ELISpot assays for IFN-γ and, depending on the number of cells available, by further exploratory assays including Intracellular cytokine staining. Further exploratory studies may include, but will not be limited to: virus inhibition assay (VIA) to assess ability of $CD8^+$ T-cells to inhibit virus replication after vaccination, epitope mapping to determine specificity, breadth and depth of the T-cell responses to HTI-encoded regions, T-cell lymphoproliferation as measured by CFSE, T-cell and serologic assays may be conducted to assess immunity to MVA and ChAdOx1. Other exploratory immunological assays including cytokine analysis, DNA analysis of genetic polymorphisms potentially relevant to vaccine immunogenicity and gene expression studies amongst others may be performed at the discretion of the Investigators. All initial investigations will be outlined in the study-specific laboratory plan. Explanatory immunology essays may be performed under the OVC Biobank ethical approval.
- **Faeces sample for the study of gut microbiota;** Faeces will be collected using specific containers following the established SOP for stool collection. After checking by the research nurses and evaluation of the Bristol scale, stool containers will be labelled and processed. Two aliquots of faeces will be stored for DNA analysis per time point and two aliquots for RNA analysis will be stored in RNA-later for subsequent microbiota analyses as outlined in the study-specific laboratory plan.

Collaboration with other specialist laboratories in the UK, Europe and outside of Europe for further exploratory tests may occur. This would involve the transfer of serum, faeces or plasma, PBMCs and/or other study samples to these laboratories for analysis, but these would remain anonymised. Informed consent for this will be gained from volunteers.

Immunological assays will be conducted according to local SOPs.

Participants will be informed that there may be leftover samples of their blood and faeces (after all testing for this study is completed). Samples sent to our collaborators outside the UK, will be destroyed after analysis. Participants will be given a separate PIS and consent form for blood and

faecal research samples remaining at the University of Oxford to be stored indefinitely in the Oxford Vaccine Centre Biobank for possible future research (exploratory immunology), including human DNA and RNA analyses to search for correlates of vaccine immunogenicity and efficacy. If a subject elects not to permit this, all of that subject's leftover samples will be discarded after the required period of storage to meet Good Clinical Practice (GCP) and regulatory requirements. All safety samples will be destroyed after analysis, in line with the Human Tissue Act 2004 and will not be stored for future research use.

7.4 Study visits

The study visits and procedures will be undertaken by one of the clinical trials team. The procedures to be included in each visit are documented in the Schedule of Procedures (Table 2). Each visit is assigned a time-point and a window period, within which the visit will be conducted.

7.4.1 *Screening visit*

All potential volunteers will have a screening visit, which may take place up to 42 days prior to vaccination. Informed consent will be taken before screening, as described in section 6.2. If consent is obtained, the procedures indicated in the Schedule of Procedures will be carried out. To avoid unnecessary additional venepuncture, if the appropriate blood test results for screening are available for the same volunteer from a screening visit for another Jenner Institute Clinical Trials group vaccine study, these results may be used for assessing eligibility (provided the result date is within the 42 days preceding enrolment in HIV-CORE 0052).

The subject's GP will be contacted with the written permission of the subject after screening to ascertain any significant medical history and as notification that the subject has volunteered for the study. The GP is not required to confirm the eligibility of the volunteer as this is solely assessed by the investigator on the basis of the medical history obtained. During screening, volunteers will be asked to provide their National Insurance or passport number so that this can be entered on to a national database which helps prevent volunteers from participating in more than one clinical trial simultaneously (www.tops.org.uk). Abnormal clinical findings from the urinalysis or blood tests at screening will be assessed as detailed in Appendix A. Abnormal blood tests following screening will be assessed according to site-specific laboratory AE grading tables which are filed in the trial master file (TMF). Any abnormal test result deemed clinically significant may be repeated to ensure it is not

a single occurrence. If an abnormal finding is deemed to be clinically significant, the volunteer will be informed and appropriate medical care arranged with the permission of the volunteer.

The eligibility of the volunteer will be reviewed at the end of the screening visit and again when all results from the screening visit have been considered. Decisions to exclude the volunteer from enrolling in the trial or to withdraw a volunteer from the trial will be at the discretion of the Investigator. If eligible, a day 0 (D0) visit will be scheduled for the volunteer to receive the vaccines and subsequent follow-up.

7.4.2 *Day 0: Enrolment and vaccination visit*

Volunteers will not be considered enrolled in the study until they have attended for their D0 visit. Before vaccination, the eligibility of the volunteer will be reviewed. Pulse, blood pressure and temperature will be observed and if necessary, a medical history and physical examination may be undertaken to determine any need to postpone vaccination/trial intervention depending on criteria listed in section 6.3.4. Blood, urine and faeces will be collected according to the Schedule of Procedures. HIV test and HIV test counselling will be performed. Volunteers will be recommended to take anti-pyretic medications before the booster vaccination (MVA.tHIVconsv3 and MVA.THIVconsv4) or soon after, if there is no clinical contra-indication. They should also been advised to take additional doses, as required, over the next 24-48 hours. Vaccination will be administered as described below.

7.4.2.1 ***Vaccination***

All vaccines will be administered intramuscularly, in the deltoid region of each arm according to SOP VC002 Vaccination, as described below in section 8.4. The injection site will be covered with a sterile dressing and the volunteer will stay in the CCVTM for observation, in case of immediate AEs. Observations will be taken 30 minutes after vaccination (+/- 5 minutes), the sterile dressing removed and injection site inspected. For the first participant in each group, observations will be taken also 60 minutes after the first (C1) vaccination (+/- 5 minutes).

Participants will be given an oral thermometer, tape measure and login details for access to an electronic diary (e-diary) with instructions on use, to record solicited AEs, along with the emergency 24 hour telephone number to contact the on-call study physician if needed. Participants will be instructed on how to self-assess the severity of these AEs.

The e-diary will collect information on the timing and severity of the following solicited AEs:

Table 3. Solicited AEs as collected on post vaccination diary cards.

Local solicited AEs	Systemic solicited AEs
Pain	Fever
Redness	Feverishness/Chills
Warmth	Joint pains
Itch	Muscle pains
	Fatigue
	Headache
	Malaise
	Nausea

Participants will be instructed on how to self-assess the severity of these AEs. There will also be space to self-document unsolicited AEs, and whether medication was taken to relieve the symptoms.

7.4.3 *Subsequent visits*

On subsequent visits, where specified in the Schedule of Procedures (section 7.1). Site personnel will:

- Review the e-diary and retain the information in the CRF
- Solicit and record local and systemic AEs
- Review and record interim medical history and concomitant medication
- Perform vital signs (pulse, blood pressure, temperature)
- Perform directed physical examination
- Assess the vaccination site
- Collect blood tests and faeces as specified in the Schedule of Procedures

7.4.4 *Final Visit*

The Final Visit or Early Termination Visit procedures will be performed according to the Schedule of Procedures (section 7.1). Site personnel will:

- Review any AEs and concomitant medications
- Perform vital signs (pulse, blood pressure and temperature)
- Perform a directed physical examination
- Assess any local and systemic reactogenicity events
- Collect blood and urine for tests as specified in the Schedule of Procedures
- HIV and STI screen and specific counselling as per Schedule of Procedure
- Perform a pregnancy test in all female volunteers where appropriate

7.4.5 *Unscheduled visits*

Visits/contacts other than those described in the Schedule of Procedures will be classified as unscheduled visits and recorded on a designated CRF. They may occur:

- For administrative reasons
- To review a laboratory investigation from a previous visit
- To review the outcome of an AE
- To conduct a study visit where a volunteer has missed the scheduled study visit window
- For any other reason requested by the volunteer or CI

7.4.6 *HIV testing and sexually transmitted infections (STI) Counselling*

Site personnel will counsel study participants about the implications of having blood tests for HIV, Hepatitis B, Hepatitis C and syphilis.

All volunteers will be assessed for HIV risk at screening, and tested for HIV antibodies as indicated in the Schedule of Procedures or as needed, if medical or social circumstances arise. All volunteers will receive HIV risk reduction counselling and pre- and post-HIV-test counselling, as specified below.

Trained and qualified study personnel will provide HIV counselling and testing at designated study visits as indicated in the Schedule of Procedures. Counselling will be provided in compliance with national guidelines.

The counselling process will, at a minimum, include information on HIV, safe sex practices and risk reduction. The objective of counselling is to ensure that volunteers have sufficient knowledge about HIV infection to understand what the test is for, the implications of a positive or negative result and the care available for HIV infection locally. Additionally, risk reduction counselling, safe sex practices, proven methods of preventing HIV acquisition and avoidance of transmission to others will be discussed with all volunteers regardless of their HIV test results.

Volunteers who are infected with HIV at screening and during follow up will be counselled and referred for care and treatment as needed. Counselling for HIV infected volunteers will include:

- Psychological and social implications of HIV infection
- Implications for sexual partners and family members
- Implications for child-bearing
- Avoidance of transmission to others in future
- Where to obtain HIV counselling, care and treatment

8. INVESTIGATIONAL PRODUCT

There are three investigational medicinal products to be studied in HIV-CORE 0052: ChAdOx1.tHIVconsv1, MVA.tHIVconsv3 and MVA.tHIVconsv4. All investigational medicinal products are manufactured under Good Manufacturing Practices and in compliance with European Union GMP guidelines.

8.1 Manufacturing and presentation

8.1.1 *ChAdOx1.tHIVconsv1*

ChAdOx1.tHIVconsv1 is manufactured by ADVENT s.r.l. registered in Italy, VAT no. IT088464101 Via Pontina km 30.600-00071 Pomezia (Rome). The drug product is formulated as a suspension for injection of intramuscular use. For use in the proposed clinical trial, the viral ChAdOx1.tHIVconsv1 drug product will be provided as a sterile virus suspension. It is a slightly opaque frozen liquid supplied at a target concentration of >1.1 x 10^{11} vp/ml. The fill volume per vial is 0.65 ml.

8.1.2 *MVA.tHIVconsv3 and MVA.tHIVconsv4*

MVA.tHIVconsv3 and MVA.tHIVconsv4 are manufactured by IDT Biologika GmbH, Am Pharmapark, D-06861 Dessau-Roβlau, Germany. MVA.tHIVconsv4 and MVA.tHIVconsv3 vaccines are presented as white cloudy solutions, formulated in Tris-saline buffer (10 mM Tris HCl, 140 mM NaCl, pH 7.7) at a concentration of 1.8x10^8 pfu/ml for MVA.tHIVconsv4 and 3.4x10^8 pfu/ml for MVA.tHIVconsv3. The extractable fill volume is 500 µl.

8.2 Supply and labelling

All the vaccines will be labelled according to EU requirements for primary and secondary labels.

8.2.1 *ChAdOx1.tHIVconsv1*

ChAdOx1.tHIVconsv1 has been formulated and vialed under Good Manufacturing Practice conditions at ADVENT s.r.l. registered in Italy, VAT no. IT088464101 Via Pontina km 30.600-00071 Pomezia (Rome). The vaccine will be certified and labelled for the trial by a Qualified Person (QP) before transfer to the clinical site. The ChAdOx1.tHIVconsv1 vaccines are supplied in standard glass vials with rubber stoppers and caps.

8.2.2 *MVA.tHIVconsv3 and MVA.tHIVconsv4*

MVA.tHIVconsv3 and MVA.tHIVconsv4 have been labelled and technically released and vialled by IDT Biologika GmbH, Am Pharmapark, D-06861 Dessau-Roβlau, Germany. The vaccines will be certified and labelled for the trial by a Qualified Person (QP) before transfer to the clinical site. The products are supplied in sterile rubber-stopped glass vials.

8.3 Storage

The vaccines are stored at a nominal ≤-65°C in a locked freezer, at the clinical site. All movements of the study vaccines will be documented in accordance with existing standard operating procedures (SOPs). Vaccine accountability, storage, shipment and handling will be in accordance with relevant SOPs and forms.

8.4 Administration

On vaccination day, vaccines will be allowed to thaw to room temperature and will be administered within 1 hour of removal from the freezer. Participants will receive two IM injections with a half dose of ChAdOx1.tHIVconsv1 into each arm at enrolment. Participants in group 2 will receive an additional two IM injections (MVA.tHIVconsv3 into one arm and MVA.tHIVconsv4 into the other arm) at the second vaccination visit. The preferred site of administration is the deltoid muscle, unless contraindicated for any reason. If the administration in one deltoid area is contraindicated, then both vaccinations will be administered in the deltoid region of the other arm. If administration in both arms is contraindicated, then vastus lateralis muscle (anterolateral thigh) of each leg can be used, at the discretion of the investigator. First participants in each group will be observed in the unit for 60 minutes (+/- 5 minutes) after vaccination and all participants will be observed for 30 minutes (+/- 5 minutes). During administration of the investigational products, Advanced Life Support drugs and resuscitation equipment will be immediately available for the management of anaphylaxis. Vaccination will be performed and the IMPs handled according to the relevant SOPs.

8.5 Minimising environmental contamination with genetically modified organisms (GMO)

The study will be performed in accordance with UK Genetically Modified Organisms (Contained Use) Regulations (2014). Approved SOPs will be followed to minimise dissemination of the recombinant

vectored vaccine virus into the environment. GMO waste will be inactivated by autoclaving according to approved SOPs.

9. ASSESSMENT OF SAFETY

Safety will be assessed by the frequency, incidence and nature of AEs and SAEs arising during the study.

9.1 Definitions

9.1.1 *Adverse Event (AE)*

An AE is any untoward medical occurrence in a volunteer, which may occur during or after the administration of an IMP and does not necessarily have a causal relationship with the intervention. An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom or disease temporally associated with the study intervention, whether or not considered related to the study intervention.

9.1.2 *Adverse Reaction (AR)*

An AR is any untoward or unintended response to an IMP. This means that a causal relationship between the IMP and an AE is at least a reasonable possibility, i.e., the relationship cannot be ruled out. All cases judged by the reporting medical Investigator as having a reasonable suspected causal relationship to an IMP (i.e. possibly, probably or definitely related to an IMP) will qualify as an AR.

AEs that may be related to the IMP are listed in the Investigator's Brochure for each product.

9.1.3 *Serious Adverse Event (SAE)*

A SAE is an AE that results in any of the following outcomes, whether or not considered related to the study intervention.

- Death
- Life-threatening event (i.e., the volunteer was, in the view of the Investigator, at immediate risk of death from the event that occurred). This does not include an AE that, if it occurred in a more severe form, might have caused death.
- Persistent or significant disability or incapacity (i.e., substantial disruption of one's ability to carry out normal life functions).
- Hospitalisation, regardless of length of stay, even if it is a precautionary measure for continued observation. Hospitalisation (including inpatient or outpatient hospitalisation for

an elective procedure) for a pre-existing condition that has not worsened unexpectedly does not constitute a serious AE.

- An important medical event (that may not cause death, be life threatening, or require hospitalisation) that may, based upon appropriate medical judgment, jeopardise the volunteer and/or require medical or surgical intervention to prevent one of the outcomes listed above. Examples of such medical events include allergic reaction requiring intensive treatment in an emergency room or clinic, blood dyscrasias, or convulsions that do not result in inpatient hospitalisation.
- Congenital anomaly or birth defect.

"Severe" is often used to describe intensity of a specific event, which may be of relatively minor medical significance. "Seriousness" is the regulatory definition supplied above.

9.1.5 *Serious Adverse Reaction (SAR)*

An AE (expected or unexpected) that is both serious and, in the opinion of the reporting Investigator or Sponsors, believed to be possibly, probably or definitely due to an IMP or any other study treatments, based on the information provided.

9.1.6 *Suspected Unexpected Serious Adverse Reaction (SUSAR)*

An SAR, the nature and severity of which is not consistent with the information about the medicinal product in question set out in the IB.

9.2 Expectedness

No IMP related SAEs are expected in this study. All SARs will therefore be reported as SUSARs.

9.3 Causality Assessment

For every AE, an assessment of the relationship of the event to the administration of the vaccine will be undertaken by the PI or a delegated clinician. An interpretation of the causal relationship of the intervention to the AE in question will be made, based on the type of event; the relationship of the event to the time of vaccine administration; and the known biology of the vaccine therapy. Alternative causes of the AE, such as the natural history of pre-existing medical conditions, concomitant therapy, other risk factors and the temporal relationship of the event to vaccination will

be considered and investigated. Causality assessment will take place during planned safety reviews, interim analyses (e.g. if a holding or stopping rule is activated) and at the final safety analysis, except for SAEs, which should be assigned by the reporting investigator.

Table 4. Guidelines for assessing the relationship of vaccine administration to an AE.

0	**No Relationship**	No temporal relationship to study product ***and*** Alternate aetiology (clinical state, environmental or other interventions); ***and*** Does not follow known pattern of response to study product
1	**Unlikely**	Unlikely temporal relationship to study product ***and*** Alternate aetiology likely (clinical state, environmental or other interventions) ***and*** Does not follow known typical or plausible pattern of response to study product.
2	**Possible**	Reasonable temporal relationship to study product; ***or*** Event not readily produced by clinical state, environmental or other interventions; ***or*** Similar pattern of response to that seen with other vaccines
3	**Probable**	Reasonable temporal relationship to study product; ***and*** Event not readily produced by clinical state, environment, or other interventions ***or*** Known pattern of response seen with other vaccines
4	**Definite**	Reasonable temporal relationship to study product; ***and*** Event not readily produced by clinical state, environment, or other interventions; ***and*** Known pattern of response seen with other vaccines

9.4 Reporting procedures for all Adverse Events (see local SOP for AE reporting)

All local and systemic AEs occurring in the 28 days following each vaccination observed by the Investigator or reported by the volunteer, whether or not attributed to study medication, will be

recorded. Recording and reporting of all AEs will take place as detailed in SOP VC027 Adverse Event Data Collection and Analysis. All AEs that result in a volunteer's withdrawal from the study will be followed up until a satisfactory resolution occurs, or until a non-study related causality is assigned (if the volunteer consents to this). SAEs will be collected throughout the entire trial period (D140).

9.4.1 *Reporting procedures for Serious AEs (see local SOP for Safety Reporting)*

In order to comply with current regulations on SAE reporting to regulatory authorities, the event will be documented accurately and notification deadlines respected. SAEs will be reported on the SAE forms to members of the study team immediately when the Investigators become aware of their occurrence, as described in SOP OVC005 Safety Reporting for CTIMPs. Copies of all reports will be forwarded for review to the CI (as the Sponsor's representative) within 24 hours of the Investigator being aware of the suspected SAE. The local safety monitor (LSM) will be notified of SAEs that are deemed possibly, probably or definitely related to study interventions; the LSM will be notified immediately (within 24 hours) of the Investigators' being aware of their occurrence. SAEs will not normally be reported immediately to the ethical committee(s) unless there is a clinically important increase in occurrence rate, an unexpected outcome, or a new event that is likely to affect safety of trial volunteers, at the discretion of the CI, following the advice of the LSM. In addition to the expedited reporting above, all SAEs will be reported in the annual Development Safety Update Report (DSUR) report. Hospitalisations for elective procedures that are planned prior to enrolment into the study will not be reported as SAEs.

9.4.2 *Reporting Procedures for SUSARS*

The CI will report all SUSARs to the MHRA and ethical committee(s) within required timelines (15 days for all SUSARs, unless fatal or life threatening in which case 7 days, with a final report within a further 8 days (total 15)). The CI will also inform all Investigators concerned of relevant information about SUSARs that could adversely affect the safety of participants. All SUSARs and deaths occurring during the study will be reported to the Sponsor. For all deaths, available autopsy reports and relevant medical reports will be made available for reporting to the relevant authorities.

9.4.3 *Development Safety Update Report*

A Development Safety Update Report (DSUR) will be submitted to the competent authority and ethical committee within 60 days of the anniversary of the first approval date from the regulatory authority for each IMP.

9.5 Assessment of severity

The severity of clinical and laboratory AEs will be assessed according to the scales in the Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events (Corrected Version 2.1, July 2017), attached as Appendix A to this protocol.

9.6 Procedures to be followed in the event of abnormal findings

Eligibility for enrolment in the trial in terms of laboratory findings will be assessed as detailed in Appendix A. Abnormal clinical findings from medical history, examination or blood tests will be assessed as to their clinical significance throughout the trial. Laboratory AEs will be assessed using the site-specific tables in the TMF. If a test is deemed clinically significant, it may be repeated, to ensure it is not a single occurrence. If a test remains clinically significant, the volunteer will be informed and appropriate medical care arranged as appropriate and with the permission of the volunteer. Decisions to exclude the volunteer from enrolling in the trial or to withdraw a volunteer from the trial will be at the discretion of the Investigator.

9.7 Interim Safety Reviews

The safety profile of the IMP will be assessed on an on-going basis by the Investigators with communication to the LSM as necessary. The CI and other relevant Investigators (as per the trial delegation log) will also review safety issues and SAEs as they arise.

9.8 Local Safety Monitor

Prof Brian Angus, a Clinical Tutor in Medicine, Honorary Consultant Physician and Director, Centre for Tropical Medicine at the University of Oxford will be appointed as an independent Local Safety monitor (LSM) to provide real-time safety oversight. The LSM will review SAEs deemed possibly, probably or definitely related to study interventions. The LSM will be notified within 24 hours of the investigators' being aware of their occurrence. The LSM has the power to terminate the study if

deemed necessary following a study intervention-related SAE. . All correspondence between investigator and LSM will be conveyed by the investigator to the trial Sponsor.

The LSM may be contacted for advice and independent review by the investigator or trial Sponsor in the following situations:

- Following any SAE deemed to be possibly, probably, or definitely related to a study intervention.
- Any other situation where the Investigator or trial sponsor feels independent advice or review is important**.**

9.8.1 *Safety Profile Review*

The safety profile will be assessed on an on-going basis by the Investigators, and at the time points dictated by the staggered enrolment. In addition, the LSM will perform independent external safety reviews after the first 5 volunteers reach day 14 and day 63. The CI and relevant Investigators (as per the trial delegation log) will also review safety issues and SAEs as they arise.

9.9 Safety Holding Rules

Safety holding rules have been developed considering the fact that this is a phase 1 study. Solicited AEs are those listed as foreseeable in the Investigator's Brochure for each product, occurring within the first 7 days after vaccination (day of vaccination and six subsequent days). 'Unsolicited AEs' are AEs other than the foreseeable AEs occurring within the first 28 days after vaccination.

9.9.1 *Re-vaccination excluding criteria*

The following AEs associated with vaccine immunisation constitute absolute contraindications to further administration of vaccine. If any of these events occur during the study, the subject must be withdrawn and followed until resolution of the event, as with any AE.

- Anaphylactic reaction following administration of the vaccine
- Pregnancy

The following AEs constitute contraindications to administration of vaccine at that point in time; if any one of these AEs occurs at the time scheduled for vaccination, the subject may be vaccinated at

a later date, or withdrawn at the discretion of the CI. The subject must be followed until resolution of the event as with any AE.

- Acute disease at the time of vaccination (defined as the presence of a moderate or severe illness with or without fever). All vaccines can be administered to persons with a minor illness such as diarrhoea, mild upper respiratory infection with or without low-grade febrile illness, i.e. temperature of < 37.7 °C / 99.9 °F.
- Temperature of ≥ 37.7 °C (99.9 °F) at the time of vaccination.

9.10.2 *Criteria for Temporary Halt of Vaccinations in All Volunteers*

All vaccinations as part of this study will be suspended (i.e. no further vaccinations will be given to any participant) if any of the following criteria arise:

1. One volunteer experiences an SAE that is possibly, probably or definitely related to the investigational product(s).

2. Two unforeseen severe AEs occur which are deemed clinically significant by the LSM. (All severe AEs will be reviewed in the study.)

3. One volunteer experiences injection site ulceration, sterile abscess or necrosis possibly, probably or definitely associated with vaccine administration.

4. One volunteer experiences a severe allergic reaction, such as laryngospasm, bronchospasm or anaphylaxis, possibly, probably or definitely associated with vaccine administration.

5. One volunteer experiences a life-threatening event or death regardless of the causality.

Vaccinations may be recommenced only if it is deemed safe to recommence by the LSM, the MHRA, the ethics committee and the study investigators following the procedures below.Procedures to follow after discontinuing vaccinations:

If vaccinations are suspended MHRA and REC will be notified within 15 days with a substantial amendment, using the notification of amendment form, clearly explaining the reason for the halt of vaccinations. In addition, the Investigators will request a review by the LSM, to be held within two business days of the Investigators learning of the event. No additional vaccinations will be given until the opinion of the LSM has been sought. However, all volunteers will remain in the study for

immunological and safety follow up. To restart vaccinations, a further request as a substantial amendment, providing evidence that it is safe to restart the trial should be made to MHRA and REC.

In addition to these pre-defined criteria, the study can be put on hold upon advice of the Local Safety Monitor, CI, Study Sponsor, Regulatory Authority, or Ethical Committee(s), for any single event or combination of multiple events which, in their professional opinion, jeopardises the safety of the participants or the reliability of the data.

10. STATISTICS

The primary objective of this study is to assess the safety of ChAdOx1.tHIvconsv1 and MVA.tHIVconsv3&4 vaccines in healthy volunteers. In total, thirteen subjects will be recruited into the study. Our experience from previous clinical trials with similar vaccines suggests that this sample size is a feasible number to recruit, screen, enrol and follow-up in practical terms, whilst also allowing the evaluation of the safety and immunogenicity of the proposed vaccine regimens.

In view of the unlikely occurrence of a SUSAR with these vaccines based on our experience of working with similar vaccines, it is not the remit of this study to recruit sufficient numbers of volunteers to be statistically confident about the efficacy results. Therefore the safety data will be primarily descriptive. The incidence of mild, moderate or severe AEs will be used as a measure of safety of the investigational products. From previous experience with similar vaccines, the proposed number of participants should be sufficient to determine the risk of serious AEs or severe local or systemic reactions in healthy volunteers.

Summary statistics will be calculated; point and interval estimates of AEs and immune responses will be reported.

Based on previous experience with similar trials, it is expected that the amount of missing, unused or spurious data will be insignificant. Unused and spurious data will be listed separately and excluded from the statistical analysis. Missing data will be excluded from the statistical analysis.

All volunteers who receive at least one vaccination will be included in the analysis.

Statistical analysis will be performed with the support of a qualified statistician based at the Primary Care trials unit, Oxford. Analysis will be conducted according to local SOPs and an agreed Statistical Analysis Plan.

11. DATA MANAGEMENT

11.1 Data Handling

The CI will be responsible for all data that accrues from the study. The data will be captured directly into the volunteers' electronic CRFs or transferred from a paper source in to the eCRF created on the study specific database. Electronic data will be stored on secure servers. Data will be entered directly into the study database via a stand-alone password protected app. The study specific database meets 21 CFR part 11 FDA standards. This includes safety data, including laboratory safety data and outcome data.

All AE data (both solicited and unsolicited) reported by the volunteer will be entered onto a volunteer's electronic diary card (eDiary) for a maximum of 28 days following administration of the IMP. The eDiary provides a full audit trail of edits and will be reviewed at each review time-points indicated in the schedule of events. Any AE continuing beyond the period of the diary will be copied into the eCRF and followed to resolution, if there is a causal relationship to the IMP, or to the end of the study if there is no causal relationship.

11.2 Record Keeping

The Investigators will maintain appropriate medical and research records for this trial, in compliance with GCP and regulatory and institutional requirements for the protection of confidentiality of volunteers. The CI, co-Investigators and clinical research nurses will have access to records. The Investigators will permit authorised representatives of the Sponsor(s), as well as ethical and regulatory agencies to examine (and when required by applicable law, to copy) clinical records for the purposes of quality assurance reviews, audits and evaluation of the study safety and progress.

With the volunteers' consent, we will keep their contact details after participation in the study is complete, so we may inform them of opportunities to participate in future vaccine related research. This will be entirely optional and participation in this study will not be affected by their decision to allow or not allow storage of their contact details beyond participation in this trial. Details will be stored electronically on a secure server and only authorised individuals at the CCVTM will have access to it. We will not, under any circumstances, share their contact details with any third party institutions without their permission. Volunteers will be informed that being contacted does not oblige them to

agree to take part in future research and they can ask us to have their contact details removed from our database at any time.

11.3 Source Data and Case Report Forms (CRFs)

All protocol-required information will be collected in CRFs designed by the Investigator. All source documents will be filed in the CRF. Source documents are original documents, data, and records from which the volunteer's CRF data are obtained. For this study, these will include, but are not limited to, volunteer consent form, blood results, GP response letters, laboratory records, diaries, and correspondence. In the majority of cases, CRF entries will be considered source data as the CRF is the site of the original recording (i.e. there is no other written or electronic record of data). In this study this will include, but is not limited to medical history, medication records, vital signs, physical examination records, urine assessments, blood results, AE data and details of vaccinations. All source data and volunteer CRFs will be stored securely.

11.4 Data Protection

The study will comply with the UK General Data Protection Regulation (GDPR) and Data Protection Act 2018, which require data to be de-identified as soon as it is practical to do so. The processing of the personal data of participants will be minimised by making use of a unique participant study number only on all study documents and any electronic database(s). All documents will be stored securely and only accessible by study staff and authorised personnel. The study staff will safeguard the privacy of participants' personal data. No information concerning the study or the data will be released to any unauthorised third party, without prior written approval of the Sponsor.

11.5 Data Quality

Data collection tools will undergo appropriate validation to ensure that data are collected accurately and completely. Datasets provided for analysis will be subject to quality control processes to ensure analysed data is a true reflection of the source data.

Trial data will be managed in compliance with local data management SOPs (including the overarching SOP OVC1913 Data and Database Management for DF/Net Studies). If additional, study-specific information is required, an approved Data Management Plan will be implemented.

12. QUALITY CONTROL AND QUALITY ASSURANCE PROCEDURES

12.1 Investigator procedures

Approved site-specific standard operating procedures (SOPs) will be used at all clinical and laboratory sites.

12.2 Monitoring

Regular monitoring will be performed according to GCP by the sponsor (CTRG). Following written SOPs, the monitor will verify that the clinical trial is conducted and data are generated, documented and reported in compliance with the protocol, GCP and the applicable regulatory requirements. The site will provide direct access to all trial related source data/documents and reports for the purpose of monitoring and auditing by the Sponsor and inspection by local and regulatory authorities.

12.3 Protocol deviation

Any deviations from the protocol will be documented in a protocol deviation form and filed in the trial master file. Each deviation will be assessed as to its impact on volunteer safety and study conduct. Protocol deviations will be listed in the end of study report.

12.4 Audit & inspection

The QA manager conducts systems based internal audits to check that trials are being conducted according to local procedures and in compliance with GCP and applicable regulations.

The Sponsor, trial sites, and ethical committee(s) may carry out audits to ensure compliance with the protocol, GCP and appropriate regulations.

GCP inspections may also be undertaken by the MHRA to ensure compliance with protocol and the Medicines for Human Use (Clinical Trials) Regulations 2019, as amended. The Sponsor will assist in any inspections and will support the response to the MHRA as part of the inspection procedure.

13. SERIOUS BREACHES

The Medicines for Human Use (Clinical Trials) Regulations contain a requirement for the notification of "serious breaches" to the MHRA within 7 days of the Sponsor becoming aware of the breach.

A serious breach is defined as “A breach of GCP or the trial protocol which is likely to effect to a significant degree

(a) the safety or physical or mental integrity of the subjects of the trial; or

(b) the scientific value of the trial”.

In the event that a potential serious breach is suspected the Sponsor will be informed as soon as possible, to allow preliminary assessment of the breach and reporting to the MHRA within the required timelines.

14. ETHICS AND REGULATORY CONSIDERATIONS

14.1 Declaration of Helsinki

The Investigators will ensure that this study is conducted according to the principles of the current revision of the Declaration of Helsinki.

14.2 Guidelines for Good Clinical Practice

The Investigator will ensure that this trial is conducted in accordance with relevant regulations and with Good Clinical Practice.

14.3 Ethical and Regulatory Approvals

Following sponsor approval, the protocol, informed consent form, participant information sheet and any proposed advertising material will be submitted to an appropriate Research Ethics Committee (REC), HRA (where required), regulatory authorities (MHRA in the UK), and host institution(s) for written approval.

No substantial amendments to this protocol will be made without consultation with, and agreement of, the Sponsor. Any substantial amendments to the trial that appear necessary during the course of the trial must be discussed by the Investigator and Sponsor concurrently. If agreement is reached concerning the need for an amendment, it will be produced in writing by the CI (or delegate) and will be made a formal part of the protocol following ethical and regulatory approval.

The Investigator is responsible for ensuring that changes to an approved trial, during the period for which regulatory and ethical committee(s) approval has already been given, are not initiated without regulatory and ethical committee(s)' review and approval except to eliminate apparent immediate hazards to the subject (i.e. as an Urgent Safety Measure).

14.4 Reporting

The CI shall submit once a year throughout the clinical trial, or on request, an Annual Progress Report to the REC, HRA (where required), host organisation, funder (where required) and Sponsor. In addition, an End of Trial notification and final report will be submitted to the MHRA, the REC, host organisation and Sponsor.

14.5 Transparency in Research

Prior to the recruitment of the first participant, the trial will have been registered on a publicly accessible database.

Results will be uploaded to the European Clinical Trial (EudraCT) Database within 12 months of the end of trial declaration by the CI or their delegate.

Where the trial has been registered on multiple public platforms, the trial information will be kept up to date during the trial, and the CI or their delegate will upload results to all those public registries within 12 months of the end of the trial declaration.

14.6 Volunteer Confidentiality

All data will be anonymised: volunteer data will be identified by a unique study number in the CRF and database. A separate confidential file containing identifiable information will be stored in a secured location in accordance with the relevant data legislation. Only the Sponsor representative, Investigators, the clinical monitor, the REC and the MHRA will have access to the records. Photographs taken of vaccination sites (if required, with the volunteer's written, informed consent) will not include the volunteer's face and will be identified by the date, trial code and subject's unique identifier. Once developed, photographs will be stored as confidential records, as above. This material may be shown to other professional staff, used for educational purposes, or included in a scientific publication.

15. FINANCING AND INSURANCE

15.1 Financing

The study is funded through the European Commission Horizon 2020 funding programme.

15.2 Insurance

The University has a specialist insurance policy in place which would operate in the event of any participant suffering harm as a result of their involvement in the research (Newline Underwriting Management Ltd, at Lloyd's of London).

15.3 Compensation

Volunteers will be compensated for their time, the inconvenience of having blood tests and procedures, and their travel expenses. They will be compensated £25 for attending the screening visit. For all other trial visits as outlined in the schedule of procedures, compensation will be calculated according to the following:

- Travel expenses:
  - £15 per visit. Where travel expenses are greater than £15 per visit because the volunteer lives outside the city of the trial site, the volunteer will be given further reimbursement to meet the cost of travel necessary for study visits.
- Inconvenience of blood tests:
  - £10 per blood donation
- Time required for visit:
  - £20 per hour

The total amount compensated will depend on the exact number of visits, and whether any repeat or additional visits are necessary.

Should the volunteer decide to withdraw from the trial before it is completed, payment will be pro rata.

15.4 Contractual Arrangements

Appropriate contractual arrangements will be put in place with all third parties.

16. PUBLICATION POLICY

The Investigators will be involved in reviewing drafts of the manuscripts, abstracts, press releases and any other publications arising from the study.

17. DEVELOPMENT OF A NEW PRODUCT/ PROCESS OR THE GENERATION OF INTELLECTUAL PROPERTY

The University will ensure appropriate arrangements are in place as regards any new IP arising from the trial. Ownership of IP generated by employees of the University vests in the University.

18. ARCHIVING

At the conclusion of the trial, research data generated during the trial will be archived in a locked built-for-purpose external archiving site.

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20. APPENDIX A DIVISION OF AIDS (DAIDS) TABLE FOR GRADING THE SEVERITY OF ADULT AND PEDIATRIC ADVERSE EVENTS

https://rsc.niaid.nih.gov/sites/default/files/daidsgradingcorrectedv21.pdf (accessed 28th July 2019).

21. APPENDIX B MODIFICATION HISTORY

VERSION	DATE	AUTHOR(S)	MODIFICATION(S)
3.0	07.04.2020	Paola Cicconi, Tomas Hanke and Andrea Baines	Section 3.3.1: Justification for nor performing toxicity study added. Section 6.3.3. Effective contraception for female volunteers amended.
4.0	07.12.2020	Paola Cicconi, Andrea Baines	Section 3.4: section on conduct of the trial during the covid-19 pandemic added Section 7.3:- text added for clarity
5.0	29.04.202	Paola Cicconi, Tomas Hanke and Andrea Baines	Synopsis: Study duration date amended Section 5.6: Text added to explain the risk of rare blood clots Section 5.6: Text added to explain the risk of interference of ChAdOx1.tHIVconsv1 with any other adenoviral-vectored vaccines administered within 3 months following ChAdOx1.tHIVconsv1 vaccination. Section 6.3.2: Additional exclusion criteria added to reflect this. Section 6.3.6: Text added to explain that participants will not be withdrawn on receipt of any other adenoviral-vectored vaccines administered within 3 months following ChAdOx1.tHIVconsv1 vaccination. Section 7: Schedule of Procedures: Additional blood sample added Section 11.1: Database access amended Section 11.4: GDPR guidelines amended to include UK Section 11.5: SOP number amended
6.0	DDMONYYYY	Molly Glaze	Section 7.4.2: Inclusion of anti-pyretic medication

		Paola Cicconi	Section 9.10.2: Amended stopping criteria