European Pregnancy and Paediatric Infections Cohort Collaboration (EPPICC) SARS-CoV-2 antibody study protocol

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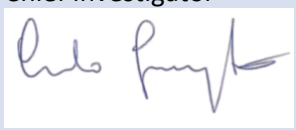
Date: **18 May 2021**

MRC CTU at UCL ID: **EPPICC SARS-COV-2**
MREC #: **X**

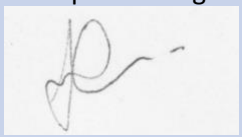
Authorised by:

Name: Professor Carlo Giaquinto
Role: Chief Investigator
Signature:



Date: 18/05/2021

Name: Dr Jeannie Collins
Role: Principal Investigator at UCL
Signature:



Date: 18/05/2021

GENERAL INFORMATION

This document was constructed using the MRC CTU at UCL Protocol Template Version 7.0. It describes the EPPICC SARS-CoV-2 antibody study, coordinated by the Medical Research Council (MRC) Clinical Trials Unit (CTU) at University College London (UCL), and provides information about procedures for entering participants into this study. Every care has been taken in drafting this protocol, but corrections or amendments may be necessary. These will be circulated to all investigators in the study, but cohorts entering patients for the first time are advised to contact the study team to confirm they have the most up-to-date version.

This protocol contains overarching guidance for the conduct of the EPPICC- SARS-CoV-2 antibody study. It should be read in conjunction with the study standard operating procedure (SOP), which provides detailed information on the data variables to be collected in the study. The Standard Operating Procedure may be updated from time to time, and study sites should ensure they refer to the most recent version. If in doubt, please contact the Study Team at MRC CTU at UCL.

COMPLIANCE

The study will be conducted in compliance with the approved protocol, the Declaration of Helsinki 1996, the principles of Good Clinical Practice, the General Data Protection Regulation and the UK Data Protection Act 2018 (DPA number: Z6364106), and the UK Policy Framework for Health and Social Care Research (where applicable) as well as all local requirements in the countries of participating cohorts.

SPONSOR

The Penta Foundation (Fondazione PENTA Onlus) is the study Sponsor and has delegated responsibility for the overall management of the study to the MRC CTU at UCL. Queries relating to sponsorship of this study should be addressed to the Penta Foundation (eppicc@pentafoundation.org; Corso Stati Uniti, 35127 Padova, Italy).

FUNDING

This study is funded by a research grant from ViiV Healthcare. The MRC CTU at UCL is supported by the Medical Research Council programme grant MC_UU_12023/26. The European Pregnancy and Paediatric Infections Cohort Collaboration is funded by grants from the Penta Foundation. The Cape Town Adolescent Antiretroviral Cohort is funded by the National Institutes of Health, USA.

STUDY ADMINISTRATION

Please direct all queries to the study co-ordinators at the MRC CTU at UCL in the first instance.

CHIEF AND PRINCIPAL INVESTIGATORS

CHIEF INVESTIGATOR (CI):

Fondazione Penta Onlus
Corso Stati Uniti,
35127 Padova,
Italy

Switchboard: +39 049 964 0122

Name: Carlo Giaquinto

Email: Carlo.Giaquinto@pentafoundation.org

PRINCIPAL INVESTIGATOR (PI):

MRC Clinical Trials Unit at UCL
90 High Holborn
London
WC1V 6LJ
UK

Switchboard: 020 7670 4700
Name: Jeannie Collins
Email: Jeannie.Collins@ucl.ac.uk

MRC CTU AT UCL: EPPICC STUDY TEAM

EPPICC PI:	Ali Judd	a.judd@ucl.ac.uk
Data Manager:	Charlotte Duff	c.duff@ucl.ac.uk
Senior Statistician:	Siobhan Crichton	s.crichton@ucl.ac.uk
Statistician:	Lizzie Chappell	e.chappell@ucl.ac.uk
Senior Epidemiologist:	Charlotte Jackson	c.r.jackson@ucl.ac.uk
Clinical Lead:	Alasdair Bamford	a.bamford@ucl.ac.uk

EXPERT ADVISORS

Immunology Lead:	Kimberly Gilmour (Great Ormond Street Hospital for Children NHS Foundation Trust, London)
Virology Lead:	Nicole Ngo-Giang-Huong (Dept. Santé et Sociétés, Institut de recherche pour le développement (IRD), France / PHPT, a collaboration between IRD and the Faculty of Associated Medical Sciences, Chiang Mai University)

CO-INVESTIGATORS

Belgium	
Tessa Goetghebuer	Hospital St Pierre, Brussels
Greece	
Vana Spoulou	Aghia Sofia Children's Hospital, National and Kapodistrian University of Athens
South Africa	
Heather Zar	University of Cape Town, Cape Town
Lisa Frigati	University of Cape Town, Cape Town
Landon Myer	University of Cape Town, Cape Town
Mary-Ann Davies	Western Cape Government: Health, Cape Town
Spain	
Marisa Navarro	Hospital General Universitario Gregorio Marañón, Madrid
Antoni Noguera	Hospital Sant Joan de Déu, Universitat de Barcelona, Barcelona
Sweden	
Lars Naver	Karolinska Institute, Stockholm

Ukraine

Alla Volokha	Shupyk National Medical Academy of Postgraduate Education, Kiev
Ruslan Malyuta	Perinatal Prevention of AIDS Initiative, Odessa

United Kingdom / Ireland (CHIPS and CHIPS+ cohorts):

Ali Judd (CHIPS and CHIPS+ overall PI)	University College London, UK
Site PIs:	
Alasdair Bamford, Sarah Johnson	Great Ormond Street Hospital for Children NHS Foundation Trust, London (CHIPS)
Julia Kenny, Daniella Chilton	Guy's and St Thomas' NHS Foundation Trust, London (CHIPS / CHIPS+)
Paddy McMaster	North Manchester General Hospital (Northern Care Alliance NHS Group), Manchester (CHIPS)
Steve Welch, Claire Robertson	University Hospitals Birmingham NHS Foundation Trust, Birmingham (CHIPS, CHIPS+)
Caroline Foster	Imperial College Healthcare NHS Trust, London (CHIPS / CHIPS+)
Sally Hawkins, Elizabeth Hamlyn	King’s College Hospital NHS Foundation Trust, London (CHIPS, CHIPS+)
Katja Doerholt, Katia Prime	St George’s University Hospitals NHS Foundation Trust, London (CHIPS, CHIPS+)

SUMMARY OF STUDY

SUMMARY INFORMATION TYPE	SUMMARY DETAILS
Acronym	EPPICC- SARS-CoV-2 antibody study
Long Title of Study	Prevalence of SARS-CoV-2 antibodies in children, adolescents and young adults living with HIV in Europe and South Africa
Version	3.0
Date	18 May 2021
MRC CTU at UCL ID	EPPICC SARS-CoV-2
REC #	17493/002
Study Design	Serial point prevalence survey
Setting	HIV clinics across Europe and South Africa.
Type of Participants to be Studied	Children and young adults living with HIV
Aim	To describe the prevalence and distribution of antibodies to SARS-CoV-2 in children and young adults living with HIV in Europe and South Africa
Sponsor	Penta Foundation
Number of Participants to be Studied	1150
Duration	18 months
Funder	Research grant from ViiV Healthcare. The MRC CTU at UCL is supported by the Medical Research Council programme grant MC_UU_12023/26. EPPICC is funded by grants from the Penta Foundation. CTAAC is funded by the National Institutes of Health, USA.
Chief Investigator	Carlo Giaquinto

LAY SUMMARY

Scientific knowledge about the COVID-19 pandemic and the virus that is causing it (SARS-CoV-2) is developing rapidly, and we have a clearer idea of the population groups who are at higher risk of becoming infected, having serious illness, and dying. However, less is known about COVID-19 in children, adolescents and young adults living with HIV. It is not yet known whether, or how, HIV affects people's risk of being infected with the virus or becoming ill. This study aims to find out whether children and adolescents living with HIV have had the COVID-19 virus, even if they did not have symptoms and did not realise it at the time.

When a person is infected with a virus, their immune system fights the infection. As a result, they produce proteins called antibodies, and it may take a few weeks for enough antibodies to be made to be detected by a blood test. These antibodies may help protect the person from getting the same infection again. In this study, we want to find out how many children and adolescents living with HIV across Europe and South Africa have antibodies to the COVID-19 virus. We want to see if the proportion with antibodies is different in younger children compared to older adolescents and young adults, and whether it varies between different countries.

Some countries are rolling out vaccines against COVID-19 and have prioritised people living with HIV. We do not know if the immune response to vaccines in people living with HIV is similar to those without HIV, how long the antibodies last for and if it varies by age or any other characteristic.

Children and adolescents with HIV regularly attend hospital outpatient appointments, and during these appointments blood samples may be taken to monitor their health. In this study, we will invite these patients to be tested for antibodies to the COVID-19 virus during their routine visit. The participants will be asked a few short questions about COVID-19 diagnoses in their household and other risk factors for exposure to the virus, and if they have been offered and received any COVID-19 vaccine. We will collect information on their HIV, medications and any other illnesses they may have. At their next routine clinic visit, approximately 6 months later, we will test them again for antibodies. Testing twice will let us see how the percentage of children, adolescents and young adults with antibodies to the COVID-19 virus has changed over time. In South Africa, HIV-uninfected adolescents from a similar socioeconomic background to those living with HIV and recruited to the study will be invited to join this study, which will allow us to compare the prevalence of antibodies across the two groups.

The information from this study will help scientists and healthcare workers care for children, adolescents and young adults living with HIV during the ongoing COVID-19 epidemic in the best possible way. Participants may be given their test results, together with information about what the result means, depending on the usual practice within their clinic.

All of the data collected in this study will be stored securely at the MRC CTU at UCL, and will conform to the General Data Protection Regulation. The results of this study will be published on Penta's public website, presented at conferences and published in Open Access scientific journals.

A Steering Committee will provide guidance for the study, to make sure the research is relevant to people living with HIV and of high quality. Patients and the public will also be involved in the conduct of the research, as many HIV clinics involve their own patients in how the studies are run, and in making sure that results are circulated widely to interested groups.

CONTENTS

ABBREVIATIONS

ABBREVIATION	EXPANSION
AIDS	Acquired Immune Deficiency Syndrome
COVID-19	Coronavirus disease 2019
DSA	Data Sharing Agreement
EPPICC	European Pregnancy and Paediatric Infections Cohort Collaboration
HIV	Human Immunodeficiency Virus
MIS-C	Multi-system inflammatory syndrome in children
MRC CTU at UCL	Medical Research Council Clinical Trials Unit at University College London
PI	Principal Investigator
PPI	Public and patient involvement
REC	Research Ethics Committee
REDCap	Research Electronic Data Capture
RNA	Ribonucleic acid
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SOP	Standard operating procedure
UCL	University College London

1 BACKGROUND

As of 14 October 2020, the WHO European region had reported over 7 million COVID-19 cases and almost 250,000 deaths [1]. At the time of initiating this study, although the number of reported cases has been lower in the African region (just over 1.2 million), likely due to both later arrival of the pandemic and incomplete reporting, over half of these have been in South Africa and over 18,000 COVID-19 deaths have been reported in the country [1].

Seroprevalence studies provide estimates of the percentage of the population that has either been infected with SARS-CoV-2 (the virus which causes COVID-19) or vaccinated against the virus, based on evidence of antibodies against the viral spike (S) or nucleocapsid (N) proteins. However, few published studies have included data from children and adolescents [2, 3]. The prevalence of antibodies to SARS-CoV-2 in children in (pre-vaccination) population studies has been estimated as ~3-4% in those aged 0-19 in Spain by mid-May 2020 [2], and 0.8% in 5-9 year-olds and 9.6% in 10-19 year-olds in Geneva by early May 2020 [3]. In England, seroprevalence in 1-24 year olds has been estimated as 5.2% (95% credible interval 3.2-7.8%) based on samples collected between May and August 2020 [4]. Whilst uncertainties remain about the extent and duration of protection that antibodies may provide, measuring seroprevalence is a first step towards understanding the proportion of a population that remains susceptible to infection and therefore the potential risk of future outbreaks.

There are currently limited and inconsistent data on the epidemiology of SARS-CoV-2 and COVID-19 in people living with HIV. The studies published to date have presented data on COVID-19 amongst adults living with HIV [5-11] but it remains unclear to what extent HIV affects the risk of infection, disease, severe disease or death. Some studies suggested that there may not an association between HIV and COVID-19 severity or mortality [5], whilst others suggest increased mortality amongst adults with COVID-19 co-infected with HIV compared to the HIV-uninfected population, even after adjustment for co-morbidities and other factors [11, 12]. These studies have not included children.

In some countries in Europe, there has been rapid scale up of COVID-19 vaccines and in the UK, persons living with HIV aged 16 years and above are included as one of the priority groups for vaccination [13]. There are very limited data on the uptake and immune response to vaccines in persons living with HIV and the duration of detectable antibodies.

Europe has some of the most well established cohorts of children born with HIV or who acquired HIV in early childhood, and many of these cohorts are part of the EPPICC (European Pregnancy and Paediatric Infections Cohort Collaboration) network, a collaborative network which combines data and expertise to answer questions about the health and care of children, adolescents and pregnant women living with HIV. EPPICC's activities include conducting the EPPICC Paediatric Study, a cohort study through which harmonised longitudinal clinical data are collected on children living with HIV. Data mergers, in which data from participating cohorts in geographically and epidemiologically diverse settings in Europe and Thailand are combined, take place approximately every 2-3 years. This allows follow-up of enrolled children to assess issues such as uptake, safety and effectiveness of novel ART drugs, and risk factors for outcomes such as clinical events and disengagement from care.

South Africa has a high prevalence of paediatric HIV, with differing epidemiology to that seen in Europe (e.g. children living with HIV in South Africa are, on average, younger than in Europe, and the prevalence of co-morbidities such as tuberculosis and malnutrition is higher in South Africa). The Cape Town Adolescent Antiretroviral Cohort (CTAAC) is a prospective cohort which follows adolescents who are infected with HIV, as well as HIV-uninfected adolescents of similar age, sex and socioeconomic background. Participants undergo a range of clinical and laboratory examinations every six months. Enrolment began at eight sites in Cape Town in 2013 and most participants are now aged 17-20 years.

Both Europe and South Africa have been heavily affected by the COVID-19 pandemic, and together these settings provide an opportunity to assess the seroprevalence of antibodies to SARS-CoV-2 in children living with HIV in settings differing in HIV epidemiology, healthcare provision and response to COVID-19 (e.g. the prevalence of risk factors for disease and the extent and duration of mitigation measures such as "lockdown"). The cohorts within EPPICC and South Africa provide a sampling frame from which to select children and adolescents living with HIV to estimate seroprevalence.

1.1 MAIN AIM

The overall aim of this study is to describe the prevalence and distribution of antibodies to SARS-CoV-2 in children and adolescents living with HIV in Europe and South Africa.

1.2 OBJECTIVES

Primary objective:

- To estimate prevalence of SARS-CoV-2 antibodies in the paediatric and adolescent HIV population and how this changes over time, overall and by key age groups and regions

Secondary objectives:

- To assess factors associated with presence of SARS-CoV-2 antibodies (including demographic factors, antiretroviral treatment, HIV-associated factors or co-morbidities and exposure to household members with COVID-19, receipt of COVID-19 vaccine)
- To estimate the incidence of changes in antibody status to SARS-CoV-2 and associated factors

2 SELECTION OF PATIENTS

2.1 INCLUSION CRITERIA

All children and adolescents attending routine HIV clinic visits will be invited to join the study if they meet all of the inclusion criteria below:

- < 18 years at HIV diagnosis
- Current age under 25 years
- Attending routine HIV care in a participating clinic
- Currently in follow-up in either CTAAC, CHIPS+ or a cohort which contributes to EPPICC
- If aged ≥16 years (or local legal adult age), willing and able to give informed consent to participate in the study
- If aged <16 years (or local legal adult age), a parent/carer able to give informed consent for participating in the study (and, depending on local requirements, those aged ≥10 years, with capacity, to also provide assent).

In addition, in South Africa HIV-uninfected adolescents will be eligible to participate in the study during planned study visits if they meet the following inclusion criteria:

- Current age under 25 years
- In follow-up in the CTAAC study
- If aged ≥18 years, willing and able to give informed consent to participate in the study
- If aged <18 years, a parent/carer is able to give informed consent for participating in the study and participant willing and able to provide assent.

2.2 EXCLUSION CRITERIA

Children and adolescents are ineligible if they:

- Are taking part in a COVID-19 / SARS-CoV-2 vaccine study at enrolment

However, should a participant who is enrolled in the EPPICC-SARS-CoV-2 study subsequently join a COVID-19 / SARS-CoV-2 vaccine study or receive a COVID-19 / SARS-CoV-2 vaccine, these are not reasons for exclusion from this study. Data will be collected on vaccine receipt and participation in vaccine studies.

At the time of writing this protocol, COVID-19 / SARS-CoV-2 vaccines are being made available at different speeds across the participating countries, so there is a possibility that study participants may receive a vaccine over the course of this study. Participation in this study must not influence or delay the choice to receive a COVID-19 vaccination, either through participation in a trial or through a vaccination programme.

2.3 INFORMED CONSENT

Participants and, where necessary, their parents / carers will be asked for informed consent before taking part in the study.

Children / adolescents and their parents / carers (as appropriate) will receive a Participant Information Sheet detailing study procedures, together with a Consent Form. To participate in the study, participants will need to:

- Agree to give a blood sample at up to two different time points, for testing for SARS-CoV-2 antibody. Participants who have previously received an antibody test as part of standard care or a research study in their clinic at least 4 months ago will be offered one additional test.
- Agree for the site investigator to determine whether the local laboratory has any stored blood samples for the participant (taken on or after 1 March 2020) and for any such samples to be tested for SARS-CoV-2 antibody
- Complete a short questionnaire at up to two different time points
- Agree to the research team collecting clinical data including on their HIV if applicable (e.g. treatment status, CD4 counts and viral loads)
- Agree to record linkage to data collected in ongoing studies in which they may be participating (e.g. EPPICC, local or national HIV cohort studies and / or local or national COVID-19 studies).

Consent may be given in person or, if clinics are operating remotely, consent may be provided via phone or video call if permitted under local guidelines and approvals.

Participants may withdraw from the study at any time without giving a reason.

Patients not consenting to participate will continue to receive their usual care in routine follow-up at the clinic. If a patient chooses not to participate in the study or subsequently withdraws, there will be no impact on their clinical care.

2.4 PARTICIPATING COHORTS

The following cohorts / clinics and PIs have expressed an interest in participating in the EPPICC serology study:

Belgium:	Hospital St Pierre Cohort, Brussels (Dr Tessa Goetghebuer)
Greece:	Paediatric Cohort (Dr Vana Spoulou)
South Africa:	Cape Town Adolescent Antiretroviral Cohort (Dr Heather Zar)
Spain:	CoRISpe-S cohort of HIV-infected children (Dr Marisa Navarro)
	CoRISpe-cat cohort of HIV-infected children (Dr Antoni Noguera)
Sweden:	Swedish Cohort Study (Dr Lars Naver)
Ukraine:	Ukraine Paediatric HIV Cohort (Dr Alla Volokha, Dr Ruslan Malyuta)
UK/Ireland:	The following clinics within the Collaborative HIV Paediatric Cohort (CHIPS) and CHIPS+ studies (overall PI: Prof Ali Judd)
	Great Ormond Street Hospital for Children NHS Foundation Trust (Dr Alasdair Bamford, Dr Sarah Johnson, Dr Kimberly Gilmour)
	Guy's & St Thomas' NHS Foundation Trust (Dr Julia Kenny, Dr Daniella Chilton)
	Imperial College Healthcare NHS Trust (Dr Caroline Foster)
	North Manchester General Hospital (Northern Care Alliance NHS Group) (Dr Paddy McMaster)
	University Hospitals Birmingham NHS Foundation Trust (Dr Steve Welch, Dr Claire Robertson)
	King's College Hospital NHS Foundation Trust (Dr Sally Hawkins, Dr Elizabeth Hamlyn)
	St George's University Hospitals NHS Foundation Trust (Dr Katja Doerholt, Dr Katia Prime)

2.5 NUMBER OF PATIENTS

A total of 1150 participants will be included. This comprises 650 participants to be enrolled from the EPPICC cohorts in Europe and 500 from the South African CTAAC cohort, which will include ~50-100 HIV uninfected participants as a comparator group. The sample size calculation is described in Section 6.1.

2.6 CO-ENROLMENT GUIDELINES

Participants should not be enrolled in this study if they are already enrolled in a SARS-CoV-2 vaccine trial at time of entry to the study. However participants included in this study may be co-enrolled in clinical trials and other studies at the discretion of the treating clinician.

Enrolment in SARS-CoV-2 vaccine studies **after** enrolment in this study is permitted and must not be influenced by participation in this study.

3 STUDY PROCEDURES

3.1 STUDY DESIGN

This is a serial point prevalence survey of representative samples of children and adolescents attending routine HIV care in the participating clinics and cohorts, with repeat antibody testing at baseline (study entry) and approximately 6 months after study entry (Table 1), and in some clinics further long-term follow-up through linkage to data collected in an ongoing longitudinal cohort study. In South Africa approximately 50-100 HIV-uninfected adolescents enrolled in the ongoing CTAAC cohort will be invited to participate in this study as a comparator group.

Eligible participants who are interested in joining the study will be asked for their consent to participate if aged ≥16 years or as per local legal requirements. For participants aged <16 years, consent of their parent/carer will be sought as per legal requirements. Assent will be sought from children and adolescents aged 10 years and older, depending on local ethics requirements. Potential participants and their parents / carers should be allowed at least 5-10 minutes to consider whether or not to take part; where possible, it may be helpful to give patients copies of the participant information sheet while they wait for their appointment.

Data collection will be conducted at HIV clinics during routine visits in clinical care (in the European cohorts) or planned study visits (in CTAAC, for both CLWHIV and HIV-uninfected adolescents), and no additional study visits will be required.

At entry to the study the participant will give a venous blood sample for a SARS-CoV-2 antibody test (the exact test used will depend on local clinical practice). An additional serum sample will be taken at the same time as a routine blood draw and leftover sample will be used if possible. At the next scheduled routine HIV clinic/study visit approximately 6 (no less than 3 and up to 13) months later, a repeat venous blood sample will be collected for a second antibody test. At each visit, participants (or their parents/carers) will be given a COVID-19 questionnaire, asking short questions about any COVID-19 diagnoses in themselves or among household members and other possible exposures to the virus. All study procedures will be carried out following local COVID-19 guidelines.

If participants have previously (after 1 March 2020 and at least four months before the date of the first sample collected as part of this study) had a blood sample tested for SARS-CoV-2 antibody as part of their routine HIV care or another research study (for which the result is available in their medical records), that test will be considered as the first test for this study. These participants would therefore provide an additional blood sample at only one study visit. Clinical data corresponding to the time of the first sample collection will be extracted.

If participants have previously (after 1 March 2020 and at least four months before the date of the first sample collected as part of this study) had blood taken for other reasons that is still stored, this may also be tested for SARS-CoV-2 antibodies. In these cases, this would be considered the first test for this study and these participants would provide an additional blood sample at only one study visit. Clinical data corresponding to the time of the first sample collection will be extracted.

Participants who are followed in cohorts which are part of the EPPICC network will continue to be followed up through the ongoing EPPICC Paediatric Study.

Table 1: Study participant timeline

	Baseline	2nd visit at 6 months*
Eligibility screen	X	
Informed consent	X	
Blood sample for SARS-CoV-2 antibody	X	X
COVID-19 patient questionnaire	X	X
Clinical data collection	X	X

* Participants who have results available from a previous blood test for SARS-CoV-2 antibody in the previous 4 months (as part of routine care or research) do not require a second test.

Participants will be given the result of their SARS-CoV-2 antibody tests with guidance on how to interpret the results, unless this conflicts with the clinic or study's usual practice.

3.2 ENROLMENT AND FOLLOW-UP

We aim to start enrolment from November 2020 (pending ethics approval) and enrol participants for approximately twelve months or until the sample size is met. The enrolment period may be extended in the event of disruptions to clinic services due to COVID-19. Where feasible, all children and adolescents meeting the inclusion criteria and attending the participating clinics during this period will be invited to take part; where this is not possible, a convenience sample of children and adolescents (e.g. those attending clinic on a specified day of the week) should be invited. The invitation to participate should be independent of the patient's probability of having been exposed to COVID-19.

Participants will be considered lost to follow-up for the purposes of this study if they have not provided the second blood sample by 13 months after the enrolment date.

Participants enrolled in the EPPICC Paediatric Study or CTAAC will continue to be followed up as part of the ongoing study.

Logs will be kept of the number of children and adolescents declining the invitation to participate, with reasons for refusal where available.

3.3 STUDY INTERVENTIONS

There are no interventions in this study. Venous blood will be taken by qualified healthcare personnel according to standard techniques used in routine care at the same time as routine blood sampling.

3.4 LABORATORY TESTING

Where sites are conducting serological testing as part of standard care, venous blood samples taken at each site will be transported to the laboratory(ies) routinely carrying out antibody testing for that site. Samples will be analysed with the tests used by each site in routine practice according to manufacturers' instructions or, if in-house tests are used, local SOPs/protocols.

At sites not offering routine serological testing, arrangements should be made with local laboratories for testing. There is strong preference for tests for IgG against the viral spike protein as data suggests this has the longest half-life; however, it is recognised that there may be local considerations influencing the range of tests available across settings and results from other tests will be considered.

Where possible, antibody test results will be reported both categorically (e.g. positive, negative, equivocal) and quantitatively (e.g. antibody titre). Results will be transferred securely as described in Section 4.2.

3.5 DISCONTINUATION OR EARLY WITHDRAWAL OF PARTICIPANTS

Participants (or their parents/carers) may withdraw from the study at any time without providing a reason.

Participants wishing to withdraw from the study will be offered two options:

1. Participants may withdraw from active follow-up (i.e. future study procedures) within this study but allow the retention and use of data already collected, and further linkage with other data sources as described in the Participant Information Sheet.

2. Participants may withdraw completely from the study, in which case all data and samples collected (if not already tested) would be destroyed and no further follow-up or linkage would take place as part of this study.

Should a participant (or their parent / carer) lose the capacity to consent, they will be withdrawn from active follow-up and their data / samples retained and included in data linkages. Participants who withdraw for any reason will not be replaced.

All withdrawals will be recorded in the study database.

3.6 SAFETY REPORTING

In this observational setting the safety reporting will follow and will be notified according to the ICH GCP and legal requirement under current national legislation.

The only procedure in this study which is additional to standard care is a blood draw, to be performed in a healthcare setting by healthcare professionals following standard methods. Safety risks to the participant are therefore minimal. Additionally, where possible, residual blood from samples taken for routine clinical care will be used, thus avoiding the need for participants to undergo a separate blood draw specifically for this study.

4 DATA COLLECTION AND MERGING

4.1 DATA COLLECTION

Collection of core data items in the main EPPICC Paediatric study for sites included in the EPPICC network is described in the main EPPICC Paediatric protocol; this includes demographic data and clinical, therapeutic, laboratory and outcome information relating to HIV, COVID-19 and multi-system inflammatory syndrome in children (MIS-C). Several identified or potential risk factors for SARS-CoV-2 infection / disease / death are included in or can be derived from the main EPPICC dataset, e.g. age, sex, ethnicity, body mass index, CD4 count, viral load, ART regimen, HCV / HBV status. These data are extracted from clinic records and submitted as part of the main EPPICC study following the study SOP, and will be linked to data collected through the serology study. If a participant is included in EPPICC and additional data are available subsequent to the most recent data submitted to EPPICC, this additional data will also be collected.
Sites which are not members of the EPPICC network will submit equivalent data relating to the time of the two study visits for CLWHIV and HIV-uninfected adolescents (Table 2).

Table 2: Summary of data to be collected at each study visit from CLWHIV and HIV-uninfected adolescents

Domain	Variables	CLWHIV	HIV-uninfected adolescents*
Study identifiers	Participant ID number, site ID	✓	✓
Demographic	Date of birth, sex, ethnicity/country of origin	✓	✓
HIV	Mode of acquisition of infection, date of diagnosis, disease stage (current and at ART initiation)	✓	
Therapeutic	Initial ART regimen and start dates, recent ART history (from start of 2020)	✓	
Co-infections	Co-infections (TB, HCV, HBV)	✓	✓
Clinical	Weight (current and at ART initiation where applicable), height (current and at ART initiation where applicable), pregnancy	✓	✓
Laboratory	Absolute CD4 counts and percentage, HIV RNA (Current and at ART initiation where applicable)	✓	
COVID-19	Suspected or confirmed COVID-19 and MIS-C diagnosis; viral genomic data; symptoms, treatments and outcomes; receipt of COVID-19 vaccines	✓	✓
SARS-CoV-2 serological test	Date of test; type of test used; result (categorical and quantitative)	✓	✓
Co-morbidities	Diabetes; asthma; cancer; renal disease / impairment; autoimmune / inflammatory conditions; history of shielding; smoking status; current or previous tuberculosis disease or infection; sickle cell anaemia; history of solid organ transplant	✓	✓
Other	Follow-up status, death, cause of death, reason for study drop-out	✓	✓

* CTAAC only

Additionally, a short questionnaire will be completed by the participant (or their parent / carer) to provide information about potential exposures to COVID-19, including diagnoses in household members and known contacts and uptake of COVID-19 vaccine.

For any participant with a record of a suspected or confirmed COVID-19 or MIS-C diagnosis, the cohort will be asked to complete an additional case record form providing details of the diagnosis (e.g. clinical features, hospital admissions, treatments and outcomes).

4.2 DATA MERGER METHODS

Individual cohorts will collect data from medical records in clinics and enter data from patient questionnaires electronically. Cohorts will then send electronic datasets to the MRC CTU at UCL, using a format and method defined in the study Standard Operating Procedure (SOP) and/or a Research Electronic Data Capture (REDCap) database. Transfer of data to the MRC CTU at UCL takes place using Galaxkey or an equivalent secure method such as UCL's REDCap server. Data are then uploaded into a customised database.

Submitted data undergo a range of logic and consistency checks. Any identified potential errors or inconsistencies are investigated through discussion between the EPPICC Paediatric Data Manager, statisticians at the MRC CTU, and individual cohorts. This may involve several rounds of queries with resubmission of data over a period of several months. When data from each site have been sufficiently cleaned, the datasets are combined into a single database.

Data may be submitted by cohorts in real time (if using REDCap) or at the end of the last patient follow-up. An initial data submission of a small number of patients may also be done early in the data collection period, to allow identification and resolution of any technical issues.

5 QUALITY ASSURANCE & CONTROL

5.1 RISK ASSESSMENT

The Quality Assurance (QA) and Quality Control (QC) considerations are based on a formal Risk Assessment, which will acknowledge the risks associated with the conduct of the study and how to address them with QA and QC processes. QA includes all the planned and systematic actions established to ensure the study is performed and data generated, documented and/or recorded and reported in compliance with the principles of Good Clinical Practice and applicable regulatory requirements. QC includes the operational techniques and activities done within the QA system to verify that the requirements for quality of the study-related activities are fulfilled. This Risk Assessment will lead to the development of a Monitoring Plan.

5.2 CENTRAL MONITORING AT MRC CTU AT UCL

Recruitment will be monitored by weekly submission of numbers enrolled via email or REDCap. This will be discussed at regular teleconferences during which any issues with recruitment will be discussed. Initially, these will be held every 2-4 weeks but may become less frequent as the study progresses.

The MRC CTU Study Team will review submitted electronic data for errors and missing data points, and consistency with previous data submissions where appropriate. An extensive series of error checks will be performed. Data queries are sent to cohorts for resolution. All submitted data, and the merged dataset, will be stored on secure servers and backed up daily. MRC CTU at UCL handling of data will follow the principles of the UK Data Protection Act.

6 STATISTICAL CONSIDERATIONS

6.1 SAMPLE SIZE

The total sample size is 1150, with provisional numbers eligible by cohort summarised in Table 3. Allowing for 70% participation, the target sample size can be met within the participating cohorts. At some sites within EPPICC, participants will receive SARS-CoV-2 serological tests as part of routine care or within an ongoing research study, and a repeat test will be offered as part of this study approximately six months after (no less than 3 and up to 13 months) the first sample; however both sets of results will be collected in this study. At other sites and in South Africa, both tests will be part of this study.

In addition, some sites may be able to test stored samples taken for other purposes and not previously tested for SARS-CoV-2 antibodies. In these cases, this would be considered the first test and the participant would have one additional test as part of this study approximately six months (no less than 3 and up to 13 months) after the first sample date.

Table 3: Provisional numbers of eligible participants (aged <25 years) per cohort

Cohort	Number of eligible participants	
	CLWHIV	HIV-uninfected adolescents
Belgium	74	0
Greece	22	0
CoRISPES (Spain)	250	0
CoRISPE-Cat (Spain)	50	0
Sweden	85	0
Ukraine	170	0
United Kingdom	442	0
EPPICC Total	1093	0
South Africa	400	50-100
Total	1493	50-100

Assuming an overall anti-SARS-CoV-2 prevalence of 10%, similar to that reported for children aged 10-19 years in Geneva, Switzerland [3], the sample size would result in a 95% confidence interval of +/-2% in Europe and +/-3% in South Africa.

6.2 ANALYSIS PLAN

Data will initially undergo extensive logic and consistency checks and any potential errors will be resolved through discussion with cohort/clinic data managers.

Proportions with SARS-CoV-2 antibody at baseline and follow-up and the number/incidence of changes in antibody status between baseline and subsequent test will be estimated overall and by key patient characteristics, region, history of symptomatic COVID-19, contact with COVID-19 cases, receipt of COVID-19 vaccine. Factors associated with the presence of SARS-CoV-2 antibody, changes in

antibody status and any subsequent COVID-19 diagnosis (if numbers allow), will be explored using univariable and multivariable logistic and Poisson regression. Exposures of interest include age, sex, ART class and regimen (e.g. protease inhibitor- or tenofovir-based versus other), CD4 count, viral load, ethnicity, BMI-for-age z-score, co-infections (e.g. tuberculosis), co-morbidities, receipt of/duration since COVID-19 vaccine and household size.

The association between HIV status and SARS-CoV-2 seropositivity, changes in antibody status and subsequent COVID-19 diagnosis will be assessed in the South African cohort (which includes HIV-uninfected children as well as CLWHIV) using similar methods. Directed acyclic graphs may be used to determine which covariates to include in the models and to aid interpretation of the results.

If there is substantial variation in the type of antibody test used (anti-S versus anti-N), analyses will be stratified by type of test. For participants with positive results at both baseline and follow-up and if data allow, quantitative antibody results will be explored to qualitatively describe the possible contribution of re-exposure boosting antibody responses (versus persistence of an existing response).

In sensitivity analyses, we will investigate the implications of misclassification of results due to imperfect sensitivity / specificity of the serological tests used.

7 REGULATORY & ETHICAL ISSUES

7.1 COMPLIANCE

The study will be conducted in compliance with the approved protocol, the Declaration of Helsinki 1996, the principles of Good Clinical Practice as laid down by the ICH topic E6 (R2), General Data Protection Regulation and the UK Data Protection Act 2018 (DPA number: Z6364106), and the UK Policy Framework for Health and Social Care Research.

Each cohort is responsible for ensuring compliance with local and national regulatory and ethical processes, and data protection.

7.1.1 DATA COLLECTION AND RETENTION

Collected data are pseudonymised: no names, initials, hospital numbers, national ID or addresses of patients are collected. All participants are assigned a unique study identification number, linkable to individual patients only by the individual cohort study staff entering the data. The Principal Investigators (PIs) of each cohort ensure that participant anonymity is maintained and that their identities are protected from unauthorised parties.

Clinical notes and administrative documentation are retained at participating centres according to local data retention and storage requirements. The MRC CTU at UCL will not receive copies (hard or electronic) of patient notes.

The study dataset will be stored at the MRC CTU at UCL, and a final copy will be sent to the study sponsor, Penta. The dataset will be held for a minimum of 5 years after the end of the study and then archived for up to 20 years initially. Although this study will end after 18 months, longer term outcomes may be ascertained through ongoing follow-up in the EPPICC cohorts (subject to funding and approvals).

Signed consent / assent forms will be stored securely at participating clinics.

7.2 ETHICS

7.2.1 COHORT ETHICS APPROVALS AND CONSENT

The study has been approved by the UCL Research Ethics Committee, subject to local approvals being obtained. Any amendments will seek further review and approval.

Individual cohorts / clinics are responsible for obtaining their own ethics and regulatory approvals to participate in this study and share pseudonymised data according to local and national regulations. Documentation of ethics approval needs to be in place prior to participation in the study and should be forwarded to the relevant project manager at the Penta Foundation (the Study Team at MRC CTU at UCL will be kept updated with the status of approvals). Country- or region-specific legislation will be followed regarding patient consent.

The Penta Foundation will periodically request documentation of the approvals, as part of governance of the study. Additionally it is necessary to show evidence of approval from time to time to third parties.

7.2.2 ETHICAL CONSIDERATIONS

Most of the data used in this study is routinely collected during participants' usual clinic visits (or planned study visits in CTAAC). Each participant will additionally be asked to complete a short questionnaire at each visit; this will be straightforward to complete and will include minimally sensitive questions (about diagnoses and exposures to COVID-19). All study procedures will be carried out following local COVID-19 guidelines.

Participants will receive an additional blood test at each of two routine clinic visits (separated by approximately 6 months). Where possible, these will be done on residual bloods, although this will not be possible if patients are not having sufficient routine bloods taken at the relevant clinic visit; in these cases an extra blood sample will be taken. Communication and discussion of the antibody test result with the participant and their parents / carers will be done according to standard practice in each cohort. Historical samples not previously tested for SARS-CoV-2 antibodies will be tested only with consent.

There is a risk that participants might feel obligated to consent due to their existing relationship with the doctor / nurse who will invite them to participate. Recruitment materials will make it clear that children and adolescents are free to decline to participate, or withdraw at any time, without affecting their clinical care.

There is a potential risk of inadvertent disclosure of HIV status to children who do not yet know their status. The participant information sheet for children has been designed to avoid any reference to HIV. In these cases, clinics will deal with these situations sensitively and ensure use of appropriate patient information sheets to avoid any unintended disclosure.

Other ethical considerations relate to ensuring confidentiality of participants in the data sharing and data storage processes. No directly identifiable data are collected as part of data mergers, and data are transferred using secure methods. All data are password protected, and have controlled access limited to authorized users only.

7.3 STUDY CLOSURE

The study will be considered closed when all participants who have not withdrawn consent have either had two blood samples analysed or been lost to follow-up. However, children enrolled in cohorts which are part of the EPPICC network will continue be followed up within the EPPICC Paediatric Study.

8 DATA SHARING

8.1 DATA SHARING AGREEMENTS BETWEEN COHORTS AND MRC CTU AT UCL

A Data Sharing Agreement (DSA) will be prepared to allow transfer of data between cohorts and the MRC CTU at UCL and a copy of the final data will be stored at the Penta Foundation. All data will be handled and used in accordance with the DSA. Cohorts should return the DSA, once signed, to the project coordinator at the Penta Foundation.

8.2 APPROACH TO SHARING DATA WITH THIRD PARTIES

Data are shared according to the MRC CTU at UCL's controlled access approach, based on the following principles:

- No data should be released that would compromise an ongoing study.
- There must be a strong scientific or other legitimate rationale for the data to be used for the requested purpose.
- Investigators who have invested time and effort into developing a trial or study should have a period of exclusivity in which to pursue their aims with the data, before key trial or study data are made available to other researchers.
- The resources required to process requests should not be under-estimated, particularly successful requests which lead to preparing data for release. Therefore, adequate resources must be available in order to comply in a timely manner or at all, and the scientific aims of the study must justify the use of such resources.
- Data exchange complies with Information Governance and Data Security Policies in all of the relevant countries.
- Shared data should be covered by an institution-level Data Sharing Agreement and papers should follow the MRC open access policy.

8.3 THIRD PARTY DATA SHARING REQUESTS

Extracts of study data may be requested for broader cohort collaboration analyses, both nationally and internationally. Requests to access study data will be considered on a case by case basis. Transfer of data (partial or complete) to third party collaborators will require approval from the PIs of cohorts contributing data (or authorised cohort representatives) and will be subject to a contract and Data Sharing Agreement, if applicable. The data transfer will be conducted through a secure process. Any data transferred to third parties must be stored by third parties in compliance with all relevant data protection regulations.

Researchers wishing to access study data should contact the Study Team in the first instance.

9 INDEMNITY

The Sponsor will perform an assessment country by country and if required by the applicable regulatory requirement(s), the Sponsor will provide insurance or will indemnify (legal and financial coverage) the investigator/institution against study subjects' claims arising from Study-related injuries, except for claims that arise from malpractice and/or negligence in respect of which the breaching party shall remain liable for such malpractice and/or negligence.

University College London does not accept liability for any breach in the hospital or clinic's duty of care, or any negligence on the part of hospital employees or other caregivers.

10 FINANCE

This study is funded by a research grant from ViiV Healthcare. The MRC CTU at UCL is supported by the Medical Research Council programme grant MC_UU_12023/26. CTAAC is funded by the National Institutes of Health, USA. EPPICC is funded by grants from the Penta Foundation.

11 OVERSIGHT & STUDY COMMITTEES

11.1 PROJECT TEAM

The Project Team consists of the Principal Investigator and key members responsible for data collection and analysis at the MRC CTU at UCL as listed in this protocol (Data Manager, Senior Statistician, Senior Epidemiologist and Clinical Lead). The Project Team oversees all aspects of the study, including data collection and submission, analysis, and reporting. It meets approximately weekly to discuss all aspects of the study; meetings may become less frequent as the study progresses.

11.2 ADVISORY GROUP

The Advisory Group will comprise representatives from each of the collaborating sites and the Project Team. Throughout the study, the Advisory Group will provide advice and feedback on the day to day running of the study at participating sites and input into decisions regarding study conduct. The Advisory Group will also be closely involved with analysis and reporting of results.

11.3 ROLE OF STUDY SPONSOR

The study sponsor, the Penta Foundation, has overall oversight of the study. Penta is responsible for documenting ethical and regulatory approvals, or waivers of these, and will hold a copy of the final study dataset.

12 PATIENT AND PUBLIC INVOLVEMENT

The Penta Foundation youth PPI group is composed of patients living with or affected by chronic infections, including HIV. Some of the collaborating sites have assembled their own youth or community advisory boards. Input from these groups – for example, regarding participant materials and research questions – will feed into study discussions of patient needs and future research directions via each site. Study findings will be shared with these PPI groups in order to disseminate results to interested communities. We have also utilised the COVID-19 PPI group at the MRC CTU at UCL.

13 PUBLICATION POLICY AND DISSEMINATION OF RESULTS

This study will follow the publication policy of the broader EPPICC study (reproduced below), which states that for specialised reports, a named authorship (where those named are members of the team which undertook the analysis and report writing) can be used after authorisation by the Steering Committee with a format as follows "Firstperson A, Secondperson B, Thirdperson C, etc … on behalf of the European Pregnancy and Paediatric Infections Cohort Collaboration (EPPICC)".

A listing of all members of the Steering Committee, key personnel and other key cohort investigators, and a link to the Penta Foundation website (https://penta-id.org/), will also be included in the Acknowledgements section. The funding paragraph of the report will refer to funding source for the specific project as well as any other relevant grants.

Abstracts for conferences will list all the members of the Project Team where possible. However, if this is not possible due to restrictions on the number of authors, abstracts will be submitted by the presenter "on behalf of the European Pregnancy and Paediatric Infections Cohort Collaboration (EPPICC)" with additional acknowledgement of South African sites as appropriate.

The results of this study will generate papers which will be submitted for Open Access publication in peer reviewed journals to ensure that study results are easily accessible to stakeholders worldwide.

Abstracts for presentations will be submitted to major national and international conferences. Study results will also be disseminated through the Penta and MRC CTU at UCL websites.

13.1 EPPICC PUBLICATION POLICY

All projects will adhere to the Uniform Requirements for Manuscripts Submitted to Biomedical Journals created by the International Committee of Medical Journal Editors ("Vancouver guidelines").

Scientific reports for public presentation which are based on the main, pre-agreed objectives of the project containing all or most of the combined dataset, should have the following group authorship and the names of members of the Project Team and Writing Group are to be listed in an appendix: "European Pregnancy and Paediatric Infections Cohort Collaboration (EPPICC)".

In rare instances and in scientific reports which are specialized in nature (i.e. methodology or novel techniques, or some PhD or MSc projects), a named authorship (where those named are members of the team which undertook the analysis and report writing) can be used after authorisation by the Steering Committee with a format as follows "Firstperson A, Secondperson B, Thirdperson C, etc … on behalf of the European Pregnancy and Paediatric Infections Cohort Collaboration (EPPICC)".

For both authorship styles, a listing of all members of the Steering Committee, key personnel and other key cohort investigators, and a link to the Penta Foundation website (https://penta-id.org/), will also be included in the Acknowledgements section. The funding paragraph of the report will refer to funding source for the specific project as well as any other relevant grants.

Writing Group members will be listed at the end of papers. The number of investigators listed per cohort on the Writing Group will primarily be based on the proportion of patients contributed by that cohort to the analysis. Cohorts contributing less than 5% of the patients (and/or follow-up time, depending on the nature of the analysis) will have one investigator per cohort, and likewise 5-9% up to two places, and 10% or more up to three places, with allowance for flexibility on a project-by-project basis. If a cohort has representation on the Project Team, that person will be counted as one

of the representatives on the Writing Group. The ordering of authorship in the Writing Group will be as follows:

- Firstly, members of the Project Team will be listed, in order of contribution
- Secondly, all Writing Group members will be listed, ordered by cohort name.

Abstracts for conferences will list all the members of the Project Team where possible. However, if this is not possible due to restrictions on the number of authors, abstracts will be submitted by the presenter "on behalf of the European Pregnancy and Paediatric Infections Cohort Collaboration (EPPICC)".

In the rare instances where a cohort has contributed data to a commissioned report which is not in the public domain (e.g. for a pharmaceutical company), and their data are subsequently excluded from the academic paper based on this work (e.g. due to slightly different inclusion criteria), they will retain co-author rights in the first academic paper from that project but not subsequent papers using the same dataset. This has happened in the case of a safety report for a pharmaceutical company, where a small number of cohorts contributed data to the report, but were subsequently excluded from the academic publication. These cohorts will be included as co-authors in the first of the academic papers, in acknowledgement of their contribution to the report, but not subsequent papers.

The results of this study will generate papers which will be submitted for Open Access publication in peer reviewed journals to ensure that study results are easily accessible to stakeholders worldwide. Previous publications arising from EPPICC include studies of timing of switch to second-line therapy [14], poor immune response in virologically suppressed children [15], and safety of specific ART drugs in routine use [16-18].

Abstracts for presentations will be submitted to major national and international conferences. Study results will also be disseminated through the Penta and MRC CTU at UCL website.

14 PROTOCOL AMENDMENTS

After the protocol has been approved by the REC no substantial amendments may be made without the documented agreement of the investigators, the Sponsor and the REC.

Date	Version	Reason	Author
3 Dec 2020	2.0	Changes requested by UCL Research Ethics Committee: - Clarified that all procedures must follow local COVID-19 guidelines - Added suggested time to consider participation - Clarified that participation must not affect receipt of COVID-19 vaccines Addition of new cohort (CHIPS+) Correction of site PI for King's College Hospital NHS Foundation Trust	Charlotte Jackson / Jeannie Collins
30 March 2021	3.0	Added REC approval number to study summary; updated Ethics section to reflect current approval status. Added CHIPS+ sites and PIs. To reflect eligibility of vaccinated participants who have previously had an antibody test prior to vaccination and use of verbal/video consent if permitted by local guidance/ethics: - Edited inclusion and exclusion criteria - Edited informed consent section - Edited co-enrolment guidelines - Edited study design section	Charlotte Jackson / Jeannie Collins

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