Mpox paediatric and adolescent clinical study

Protocol version & date: v1.0 9th February 2023

Authorised by:

Name:	*Zoi Dorothea Pana*
Role:	Co-Chief Investigator
Name:	*David Aguilera-Alonso*
Role:	Co-Chief Investigator
Name:	*Charlotte Jackson*
Role:	Co-Chief Investigator/Statistician
Name:	*Laura Mangiarini*
Role:	Sponsor Representative

PROTOCOL AMENDMENTS HISTORY

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

Date	Version	Rationale	Author

CONTACT DETAILS

SPONSOR

Name:	Fondazione Penta Onlus	***Switchboard:***	+39 049 964 0122
Address:	Torre di Ricerca Pediatrica, Corso Stati Uniti, 4, 35127	***Fax:***	+39 049 964 0123
City:	Padova		
Country	Italy		

Fondazione Penta Onlus Staff

Clinical Project Manager	*Giorgia Dalla Valle*	***Email:***	giorgia.dallavalle@pentafoundation.org
REDCap Data manager	*Andrea Oletto*	***Email:***	andrea.oletto@pentafoundation.org
Data manager	Luca Stona	***Email:***	luca.stona@pentafoundation.org

CHIEF INVESTIGATORS

Co-Chief Investigator	*Zoi Dorothea Pana*	***Institution:***	Medical School, European University Cyprus
		Email:	Z.pana@euc.ac.cy
Co-Chief Investigator	*David Aguilera-Alonso*	***Institution:***	Hospital General Universitario Gregorio Marañón, Madrid, Spain.
		Email:	david.aguilera@salud.madrid.com
Co-Chief Investigator and study statistician	*Charlotte Jackson*	***Institution:***	MRC Clinical Trials Unit at UCL, University College London, UK.
		Email:	c.r.jackson@ucl.ac.uk

FUNDER This study is funded by Horizon Europe under the Grant Agreement No. 101045989 as part of the VERDI (SARS-CoV2 variants Evaluation in pRegnancy and paeDIatrics cohorts) project.

CLINICAL STUDY SIGNATURE PAGE

Sponsor:

Signature

Feb 10, 2023
Date of Signature

Name Laura Mangiarini
Title Chief Program Officer
Institution Fondazione Penta Onlus

Co-CIs:

Signature

Feb 16, 2023
Date of Signature

Name Zoi Dorothea Pana
Title Co-CI
Institution Medical School, European University Cyprus

Signature

Feb 10, 2023
Date of Signature

Name David Aguilera-Alonso
Title Co-CI
Institution Hospital General Universitario Gregorio Marañón, Madrid, Spain

Signature

Charlotte Jackson
Charlotte Jackson (Feb 13, 2023 09:38 GMT)

Feb 13, 2023
Date of Signature

Name Charlotte Jackson
Title Co-CI
Institution MRC Clinical Trials Unit at UCL University College London, UK

TABLE OF CONTENTS

1 BACKGROUND AND RATIONALE 6

2 AIM AND OBJECTIVES 7

2.1 Primary objectives 7
2.1.1 Phase 1 registry 7
2.1.2 Phase 2 observational study 8
2.1.3 Phase 3 nested sub studies 8

3 STUDY DESIGN 9

3.1 DESIGN 9

3.2 STUDY TIMELINES 10

4 ELIGIBILITY CRITERIA 10

4.1 INCLUSION CRITERIA 10

5 STUDY PROCEDURES AND SITES 11

5.1 STUDY SITES 11

6 DATA MANAGEMENT 12

6.1 RedCAP 12

6.2 CONFIDENTIALITY 13

6.3 DATA HANDLING 13

6.4 STUDY RECORDS RETENTION 13

7 STATISTICAL CONSIDERATIONS 14

7.1 OUTCOME MEASURES 14

7.2 SAMPLE SIZE 14

7.3 ANALYSIS PLAN 14

8 ETHICAL AND REGULATORY ISSUES 15

8.1 COMPLIANCE 15
8.1.1 Study Compliance 15
8.1.2 Site Compliance 15

8.2 ETHICAL CONDUCT OF THE STUDY 15

8.3 INFORMED CONSENT 15

8.4 DIRECT ACCESS TO SOURCE DATA 16

8.5 STUDY TERMINATION 16

9 OVERSIGHT AND STUDY COMMITTEES 17

10 FINANCIAL DISCLOSURE 18

11 PUBLICATION AND DATA SHARING POLICY 19

12 REFERENCES 20

1 BACKGROUND AND RATIONALE

Historically, mpox [1] (previously known as monkeypox or MPX) has occurred in children and adolescents (as well as adults) living in endemic regions. Although the clinical presentation is expected to be similar in children as in adults, it is not known whether children are at greater risk of infection, disease, or severe outcomes. Rare complications of mpox include encephalitis, cellulitis, pneumonia, sepsis, abscess, airway obstruction due to severe lymphadenopathy, keratitis, and corneal scarring [2].

Vertical transmission of mpox virus has been documented [3, 4], but the natural history of congenital mpox is unknown. It is also noted that immunocompromising conditions and certain skin conditions, such as eczema, are associated with increased severity of mpox disease in adults and children, although there are limited data on risk factors for infection specifically amongst children and adolescents.

To date, the only antiviral drug licensed for treatment of mpox is tecovirimat. This is available in some countries for treatment of mpox in adults and children weighing more than 13 kg, but data on effectiveness in humans (and particularly children) are limited. There are currently no data on post-exposure and pre-exposure prophylaxis (PEP/PrEP) to prevent mpox in children, and there are no vaccines or other products currently licensed for mpox prevention in children or adolescents. The state of knowledge regarding this infection and its associated disease in these groups is limited and, considering the 2022 global outbreak and potential for ongoing transmission, it is crucial to rapidly collect harmonised data to better define the disease course and characteristics and identify any changes in epidemiology and variations between settings.

To date, no harmonized European or global paediatric clinical protocol for data collection and follow-up of children and adolescents diagnosed with mpox has been established and there are currently very limited data on the efficacy and safety of interventions for the treatment and prevention of mpox, including vaccines, for children and adolescents. The lack of a common protocol hampers the response to the outbreak, for two reasons. Firstly, to date, numbers of children and adolescents diagnosed with mpox have been small. Second, outputs from different studies and systems may be difficult to compare due to differences in factors such as study design, data collected, and variable definitions; synthesising this disparate evidence to inform policies regarding treatment and mitigation measures is then extremely challenging.

The primary objective of this study is to use a harmonised data collection system to describe the presentation, clinical course and outcomes of laboratory-confirmed mpox virus infection in infants, children and adolescents. Such a protocol can be used for purposes of surveillance and assessment of clinical symptoms, severity of disease and effects of treatment. In the future, if vaccines become more widely used in children and adolescents, it will also allow preliminary assessment of vaccine effectiveness. Finally, the data collected can also serve as a sampling frame from which to recruit participants into additional studies, for example of vaccine immunogenicity and safety, and trials.

The involvement of sites from different settings will enable capture of any epidemiological differences associated with factors such as geographic location, country income, and mpox endemic status. Physicians from participating sites will also be encouraged to report to relevant authorities any adverse events potentially related to any intervention used in routine care, where possible including an assessment of causality. This will be helpful in better defining the safety profiles of these interventions.

The longer-term intention is that this protocol and database will be adapted and used for other emerging or re-emerging infections in children, where case numbers may initially be low, warranting a centralised repository approach.

2 AIM AND OBJECTIVES

The overall aim of this study is to increase knowledge about mpox infection and its associated disease in infants, children and adolescents. This will be done through the development of a harmonized system that will allow collection of information on demographics, clinical symptoms, clinical course, treatments and outcomes.

The study will be carried out in three potential phases:

- ***Phase 1:*** rapid development of an online paediatric registry for collection of data on mpox in infants, children and adolescents. This will allow harmonised collection of anonymised routine clinical data on infants, children and adolescents with laboratory-confirmed mpox infection, including adolescent girls who acquired mpox in pregnancy, and infants who acquired mpox through vertical transmission. Data to be collected include clinical characteristics, disease severity, treatments received and outcomes. All data will be fully anonymised, allowing rapid implementation in many countries without the need for ethics approval, where applicable.
- ***Phase 2:*** if more detailed prospective data collection would aid the public health response, an enhanced observational study of infants, children and adolescents with confirmed mpox infection (as in Phase 1) will be established. This will be a consented study collecting detailed pseudonymised data over the course of the infection. The decision about whether to carry out phase 2 will be based on the ongoing case numbers and the existence of other surveillance systems/studies.
- ***Phase 3:*** initiation of nested sub-studies within the consented observational study (Phase 2) to investigate specific research questions in this population, including collection of samples, where necessary, for analysis and/or storage in a biobank. Each sub-study will require its own protocol and informed consent.

The database, networks and systems developed within Phases 1 to 3 will be flexible and designed to be readily adapted to data collection for other emerging and re-emerging infections in children.

2.1 PRIMARY OBJECTIVES

2.1.1 Phase 1 registry

- To describe anonymised data on paediatric and adolescent patients with mpox infection to inform approaches to infection control and prevention during this and future outbreaks, depending on case trajectories, with flexibility to adapt to other (re-) emerging infections in the future. Depending on the numbers reported, this may include:

    a. monitoring the temporal and geographical distribution of mpox infection in the paediatric and adolescent population, including in specific paediatric/adolescent groups, such as those with underlying conditions or with vertically acquired mpox;

    b. describing the epidemiology and clinical presentation of the infection/ disease, including outcomes of treatment administered as part of routine care;

    c. describing the populations at highest risk of severe outcomes, including identifying factors associated with severe disease and death;

    d. describing characteristics and outcomes of infants with vertically acquired mpox infection.

2.1.2 Phase 2 observational study

- To describe pseudonymised data on paediatric and adolescent patients with mpox infection in terms of presentation, clinical course, and outcomes. Depending on the numbers reported, this may include:

    a) monitoring the temporal and geographical spread of cases of mpox infection in the paediatric and adolescent population, including in specific paediatric groups, such as those with underlying conditions;

    b) describing the epidemiology and clinical presentation of the infection, including outcomes of treatment administered as part of routine care;

    c) describing the populations at highest risk of severe outcomes, including identifying factors associated with severe disease and death;

    d) among mpox patients who are pregnant, describing the infection status of offspring (and estimating vertical transmission risk, if feasible), and characteristics and outcomes of infants with vertically acquired mpox infection.

The Phase 2 consented study will allow collection of pseudonymised data allowing more detailed analyses than are possible in Phase 1 (unconsented and anonymised).

2.1.3 Phase 3 nested sub studies

Each nested sub study implemented in Phase 3 will have its own objectives and protocol.

3 STUDY DESIGN

3.1 DESIGN

This is a multicentre, observational study on mpox in infants, children and adolescents which involves European and non-European countries.

The study includes three phases (described above), of which this protocol describes Phases 1 and 2.

Phase 1 registry.

An online registry will be developed to collect anonymised routine clinical data on patients with laboratory confirmed mpox infection aged <18 years. This may include pregnancy and neonatal data both for adolescents who are pregnant or up to 28 days postnatal and have mpox, and infants diagnosed with mpox in the neonatal period. Because all data collected will be fully anonymised, ethics approval may not be required in some or all countries, allowing swift implementation of the registry in response to an outbreak.

Data to be collected include clinical characteristics, symptoms and disease severity, treatments received and outcomes. Data for each patient will be reported at a single point in time, at the end of the clinical episode (e.g. at discharge from care). Data will be collected on historic cases (occurring before the inception of the registry), and on incident cases where relevant approvals and/or consent have not been obtained for Phase 2. Only routinely collected clinical data will be reported.

Phase 2 observational study.

When Phase 2 is activated, it will be implemented at each participating site when all required approvals are in place . Phase 2 consists of the development of a prospective observational study which will collect the same data as for the Phase 1 registry, as well as additional data such as dates of events and date of birth which are considered pseudonymised data. For this reason, informed consent/assent will be required from participants and/or their legal guardian. Patients (and/or their legal guardian) may be asked for permission to link their data to other medical records, and to be contacted for further research studies.

If the patient/legal representative does not give consent to participate in Phase 2, the study team will proceed with entering data only into the Phase 1 anonymous registry database.

The eCRF will be based on routine patient visits, and all visits from initial presentation (diagnosis or admission) onwards (follow-up visits) will be entered, until the infant, child or adolescent is considered fully discharged from care (outcome visit). Follow-up of infants born to adolescent mothers who acquired mpox in pregnancy to ascertain neonatal outcomes should end at or before day 28 after the baby is born. If consent is sought for collecting detailed information on infants who acquired mpox and whose mothers are already recruited in the study, linkage of maternal study ID and infant study ID will be made (see section 6.1 for more details).

Only routinely collected clinical data will be entered in the database.

3.2 STUDY TIMELINES

The study will aim to collect all data over approximately 18 months.

Study activity*	**Project Month (calendar month) ****
M24 Paediatric registry online (Phase 1 start)	12 (Oct 2023)
Del 7.15 Study initiation package	16 (Feb 2023)
Database Phase 2 go live (Phase 2 start)	The decision about whether to carry phase 2 will be based on an assessment of ongoing case numbers and the existence of other surveillance systems/studies.
Interim analysis	22 (Aug 2023)
Del 7.16 Midterm recruitment report	24 (Ott 2023)
Final analysis	45 (July 2025)
D 7.18 Report on status of posting results (Final report)	48 (Oct 2025)

* Month numbers measured from start of VERDI project (November 2021).

**VERDI project timelines are reported in *italics*.

4 ELIGIBILITY CRITERIA

All patients with laboratory-confirmed mpox infection seen in hospitals as well as primary/ community care settings will be eligible for inclusion in Phases 1 and 2.

4.1 INCLUSION CRITERIA

For the Phase 1 registry all infants, children and adolescents aged <18 years at the time of mpox diagnosis, with laboratory-confirmed mpox infection, as per national guidelines, will be eligible for inclusion in the anonymised dataset. Moreover, mothers of eligible infants who are diagnosed with mpox at 28days or less are included in the study to collect maternal data on pregnancy and delivery..

For the Phase 2 observational study all patients meeting the inclusion criteria for Phase 1 will be eligible for inclusion. Patients and their legal guardians will be required to give informed consent/ assent.

5 STUDY PROCEDURES AND SITES

For Phases 1 and 2, there will be no change to patient care as a result of inclusion in the study; data will be collected on clinical status, treatments received, and outcomes as recorded in routine care and not according to a defined schedule of procedures.

Phase 1 will collect basic, routine and anonymised data. Where required, each site will be responsible for seeking the country-appropriate ethics approvals or waivers, and it is expected that most will be granted waivers or provide evidence that approval is not required. The link to the online data capture system will be shared through existing networks of clinicians and researchers working in related areas, with an invitation to enter details on all cases of mpox infection aged <18 years seen in their centres. This will include retrospective entry of cases seen before activation of the data entry system as well as incident cases, where approvals are not yet in place for Phase 2, or participants have not consented to Phase 2. Summary data will be entered at the end of each patient's clinical episode.

Patients already entered into the Phase 1 database will not be contacted to give their consent to join Phase 2, to avoid duplication.

For **Phase 2**, patients and (where appropriate) their legal guardians will be informed about the study and asked for consent / assent to take part (see further details in Section 8.3: Informed Consent). Consent can be sought at any point from first presentation (at diagnosis or admission) of the patient until discharge from care. Where consent is given, the 'Initial Presentation Form' in REDCap should be completed as soon as possible and thereafter, each site can decide to perform the data entry following each patient visit or at the point of patient discharge from care. Longer term follow-up or enhanced data collection may be enabled through linkage to routine data sources (e.g. hospital and primary care records), if additional consent is granted.

Where consent is not given for Phase 2, anonymised data will be entered as in Phase 1 (if permitted under local ethics requirements).

Specific study procedure relevant to **Phase 3** will be detailed in the appropriate sub study protocol.

5.1 STUDY SITES

Phase 1 of the study will be cascaded through VERDI, Penta and VACCELERATE networks (in endemic and non-endemic countries). Additionally, Phase 1 will be advertised to other national and international networks, in order to increase the representation of further countries. Sites will be provided with log-in details enabling entry of anonymous information into the REDCap server following confirmation by the Sponsor of receipt of appropriate approvals, waivers, or evidence confirming that approvals are not required.

For Phase 2 the Sponsor will be conducting site feasibility assessments and selection according to presence of cases, willingness to be involved and appropriate resources at site level to gain approvals and enter data. The Sponsor will provide sites with the study documents (inclusive of Patient Information Sheet, Consent forms, privacy notice and CRF forms) for ethics submissions.

6 DATA MANAGEMENT

6.1 REDCAP

Source documents are represented by documents where data are first recorded, and from which participants' electronic case report forms (eCRF) data are obtained. These include, but are not limited to, hospital records (from which medical history and previous and concurrent medication may be summarised into the CRF).

In this study, primary data sources are collected in eCRFs completed by study staff at participating sites. Source data will be collected directly into a web-based REDCap database specifically designed by the study team. A separate but interoperable REDCap database will be developed for each phase: 1) the unconsented, anonymised data, 2) consented, pseudonymised data, and 3) each additional sub study initiated in Phase 3 (each to be described in its own protocol).

To enhance accuracy, data will be subjected to logic and consistency checks, e.g., for implausible values and inconsistencies. Potential errors will be investigated and discussed between the data manager, statisticians, and individual sites.

In Phase 1, data for each patient will be entered at the end of clinical follow-up and each clinical site will transcribe into the eCRF only anonymous retrospective data from source data. No personal identifiable data will be entered into the eCRF (e.g., date of birth will be replaced with age group at diagnosis).

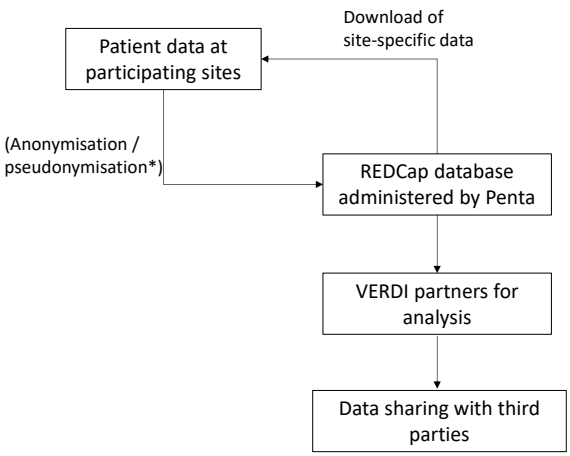
In Phase 2, pseudonymised data will be collected. The 'Initial Presentation Form' in REDCap should be completed as soon as possible and thereafter, each site can decide to perform the data entry following each patient visit or as in Phase 1, at the point of patient discharge from care.

In Phase 1 data will be fully anonymous therefore no identifiers will be recorded, whereas in Phase 2 the participants will be identified by a unique study-specific number and/or code in any database. The name and any other identifying detail will be retained only by the site staff on the consent form and the clinical records.

Phase 2 maternal-infant record linkage: If consent is sought for collecting detailed information on an infant with mpox whose adolescent mother has mpox and is already recruited in the study, the mother's study ID should be reported by the study staff on the newly generated infant record, to allow for linkage of maternal study ID and infant study ID.

Data may be shared with third parties subject to appropriate Data Sharing Agreements, with requests for access to data reviewed in accordance with the VERDI Data Management Plan (see further details in Section 10).

The diagram below illustrates the data flow for the study.



*Unconsented data will be fully anonymised; consented data will be pseudonymised

6.2 CONFIDENTIALITY

All information collected on participants will remain strictly confidential and anonymous (in Phase 1) or pseudonymised (in Phase 2). Access to data is only allowed by people mandated by the Sponsor and involved in the progress of the project, as well as representatives of regulatory authorities in order to check collected data accuracy. For pseudonymised data, the identification key (linking study ID numbers to participants' names and / or contact details) will be retained by each site entering data.

6.3 DATA HANDLING

The electronic case report forms will be hosted on a secure, web-based REDCap instance, hosted by the Sponsor. Access to the study database will require unique usernames and passwords, issued by the study Sponsor only to staff mandated by the Sponsor and duly trained to Good Clinical Practice (GCP) and General Data Protection Regulations (GDPR) standards. All data entries and edits will be fully auditable. Access to view and extract data from the REDCap electronic case report form, both the anonymised (phase 1) and the pseudonymised (phase 2) datasets will granted to specific study personnel at MRC Clinical Trials Unit at UCL, where the statistical data analysis will be carried out. After the analysis, data will be stored by the Sponsor for a minimum of fifteen years. All transfer of data will be subject to appropriate data sharing agreements.

Data security will be managed by Penta according to the CSI security standards to guarantee confidentiality, integrity and availability in line with GCP and GPP.

6.4 STUDY RECORDS RETENTION

Each participating site will maintain appropriate medical and research records for this study, in compliance with International Council on Harmonisation (ICH) GCP and regulatory and institutional requirements for the protection of confidentiality of participants.

Essential documents must be retained for a minimum of fifteen years and for as long as required by law as maximum, after the conclusion of the Study.

The Investigator must notify the study Sponsor if he/she wishes to remove the essential documents to another location or is unable to retain them for a specified period. The Investigator must obtain approval in writing from the Sponsor prior to destruction of any records. If the Investigator is unable to meet this obligation, the Investigator must ask the Sponsor for permission to make alternative arrangements. Details of these arrangements should be documented.

7 STATISTICAL CONSIDERATIONS

7.1 OUTCOME MEASURES

Phases 1 and 2 will describe clinical symptoms, treatments received, and outcomes including complications, need for hospitalisation, ICU admission or support, use of interventions such as pain management, long term sequelae.

7.2 SAMPLE SIZE

In Phase 1, the preliminary analysis will be largely descriptive. Therefore, no formal sample size calculation has been undertaken, and instead all available data on cases will be utilised. Future specific analyses in Phases 1 and 2 will be assessed for feasibility based on the numbers of cases reported and their characteristics (e.g. numbers with and without a particular exposure of interest, such as age or vaccination).

7.3 ANALYSIS PLAN

Analysis of the data collected in Phases 1 and 2 will be primarily descriptive, including summaries of:

- Age, sex/ gender, temporal and geographical distribution of children and adolescents with laboratory-confirmed mpox infection
- Description of clinical symptoms, including number of lesions
- Frequency of specified outcomes, including proportion hospitalised and admitted to ICU
- Likely mode of mpox acquisition
- Treatments administered, including use of tecovirimat, its duration and outcomes following treatment
- Number of infants with congenital infections, and description of maternal and infant characteristics

If numbers allow, additional analyses will assess the association between patient characteristics / interventions and outcomes, for example comparing the odds of severe outcomes between patients who did and did not receive specific antiviral treatments or who were versus were not vaccinated, using multivariable logistic regression.

8 ETHICAL AND REGULATORY ISSUES

8.1 COMPLIANCE

8.1.1 Study Compliance

The procedures set out in this study protocol are designed to ensure that Sponsor and Investigator abide by GCP, as described in ICH Guideline E6 and in accordance with the general ethical principles outlined in the Declaration of Helsinki. Each phase of the study will receive approval or waiver from each participating site IRB/EC prior to commencement.

8.1.2 Site Compliance

The site staff will conduct all aspects of this study in accordance with GCP; Declaration of Helsinki, applicable data protection laws and regulations applicable to the study in jurisdictions in which the Investigator conducts the study.

The site investigator is responsible for keeping records of all individuals who participate in the study and sign an informed consent form (when applicable).

All documents and information related to the protocol cannot be publicly available without express written approval from Sponsor. Only information that is previously disclosed by Sponsor on a public registry website may be freely disclosed by the Investigator or its institution, or as outlined in the Clinical Study Agreement.

At the time results of this study are made available to the public, the Sponsor will provide investigators with a summary of the results. The investigator is responsible for sharing these results with the participants and/or their caregiver (for participants providing pseudonymised data).

8.2 ETHICAL CONDUCT OF THE STUDY

This study will be submitted for approval by Research Ethics Committees (REC)/Institutional Review Boards (IRB)/local Ethics Committees in each of the participating countries, where required. Prior to initiation of each phase of the study at each site, the site must provide to the Sponsor a copy of the written EC/IRB approval of the protocol and study documents (e.g. Participant informed consent forms, patient information sheet etc.), waivers, or evidence confirming that approvals are not required.

The approval letter will be identified by protocol number, title, date and version number. The investigators will receive all the documentation needed for submitting the present protocol to the REC. If the approval is suspended or terminated by the REC, the investigators will notify the Sponsor immediately.

8.3 INFORMED CONSENT

Written informed consent to enter into the Phase 2 study must be obtained from parent/legal guardian before any data are entered into the database; children / adolescents may also consent themselves without legal guardian consent where this is permitted under national regulations. Children deemed able to understand the study should give assent according to national regulations/guidelines, those who do not assent must not be included in the study. A specific consent will be sought from mothers of infants diagnosed with mpox at 28 days of life or less, to collect pregnancy and delivery data relating to the birth of the infant. Moreover, adolescent girls who acquired mpox in pregnancy (and/or their legal guardian) will be asked consent/assent to share additional information related to pregnancy and delivery outcomes.

Signed study consent and assent forms must be kept by the investigator in the Investigator Site File, a copy must be kept in the child's medical record and a copy given to the participant or family.

If the child and/or the parent/legal guardian is illiterate but gives oral assent, a literate witness must sign the consent form instead. Participants who are illiterate should include their thumb print as well.

Participants (or parent/legal guardian of a child) must be informed that participation is voluntary and that they may withdraw from the study at any time, without prejudice. The rights and welfare of the participants will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study.

8.4 DIRECT ACCESS TO SOURCE DATA

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

8.5 STUDY TERMINATION

The Sponsor reserves the right to terminate this study prematurely at any time for reasonable administrative reasons. Any premature decision will be appropriately documented according to local requirements.

In addition, the Investigator or Sponsor has the right to discontinue a single site at any time during the study for medical or administrative reasons such as:

- GCP noncompliance
- Inaccurate or incomplete data collection
- Falsification of records

9 OVERSIGHT AND STUDY COMMITTEES

The Study Management Team (SMT) consists of the study Co-Chief Investigators, Clinical Project Manager, Epidemiologist, Statistician, Data Management Team and the VERDI Project Manager. This team oversees the day to day running of the study and meets regularly to discuss all aspects of the study. The VERDI Project Steering Committee will be contacted if relevant issues arise and the SMT will feed back as appropriate to the VERDI Project Steering Committee via the Work Package 7 lead.

New analyses, whose purposes are compatible with the ones pursued in the study, may be proposed using the VERDI Concept Sheet by contacting the VERDI study team.

10 FINANCIAL DISCLOSURE

This study is part of the VERDI project which is funded through the Horizon EUROPE programme.

11 PUBLICATION AND DATA SHARING POLICY

The VERDI publication policy will be made available to all sites and researchers participating in the study.

The study will be registered on clinicaltrials.gov, details of the study protocol and study results will be made available on the portal.

Any third-party requests to access data from the study will be handled in line with the VERDI Data Management Plan.

12 REFERENCES

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MPX study_Verdi_ Penta Foundation Protocol_v 1.0_20230209

Final Audit Report 2023-02-16

Created:	2023-02-10
By:	Anna Ferrario (administration@pentafoundation.org)
Status:	Signed
Transaction ID:	CBJCHBCAABAABvStdC18zlQMaoN1smlb-LtEdv5zdjDQ

"MPX study_Verdi_ Penta Foundation Protocol_v1.0_20230209" History

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