

# Mpox Clinical Characterisation Protocol (Nigeria)

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# **1 Background and Objectives**

## **1.1 Purpose of the Study**

This is a protocol for the rapid, coordinated clinical research-based investigation of human mpox virus (hMPXV) infection (mpox) in Nigeria. It is based on the International Severe Acute Respiratory and emerging Infections Consortium (ISARIC) Clinical Characterisation Protocol (CCP) for pathogens of public health concern. Specifically, it is adapted from the ISARIC/WHO CCP-UK protocol, v10.2, 15th September 2022.

By necessity this protocol is flexible and comprehensive. A supplementary guidance document will be used to define the actual sampling frequency and specific samples in use for each site in Nigeria. The Case Report Form (CRF) used for data collection is based on the ISARIC CCP CRF, adapted for studying individuals with mpox in Nigeria.

Patients with a diagnosis of mpox will be recruited. This protocol has been designed to maximize the likelihood that data and biological samples are prospectively and systematically collated and shared rapidly with clinicians, public health agencies and policy makers in a format that can be easily understood and then aggregated, tabulated, and analysed across many different settings both nationally and globally.

The protocol is designed to have flexibility to ensure the broadest acceptance. The ISARIC protocol on which it is based was developed in response to cases of Middle Eastern Respiratory Syndrome coronavirus (MERS-CoV) in 2012-2013, Influenza H7N9 in 2013, viral haemorrhagic fever (Ebola virus) in 2014, mpox & MERS-coronavirus in 2018, Tick-borne encephalitis virus (TBEV) in 2019, Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) in 2020 and in 2022 mpox, Lassa fever, and severe hepatitis of unknown origin in children.

The study is supported and managed by Nigeria Centre for Disease Control and Prevention (NCDC), as part of a research package for mpox in Nigeria, and in collaboration with the UK Public Health Rapid Support Team (UK PHRST), the London School of Hygiene and Tropical Medicine, and the University of Oxford.

### **1.1.1 Preliminary, retrospective data pilot**

To test the study CRF and data collation process, an internal pilot will be performed using clinical data from mpox patient-cases in 2022/3 already collected into Public Health case investigation forms (CIFs) and held by NCDC. The aim is to test data availability from secondary care and primary care sources and ensure the design of the CRF is appropriate and realistic, ensuring that essential data are captured, and that superfluous data fields are identified and removed to improve efficiency in the subsequent, prospective study. This pilot will not require any direct interaction with patient-cases; it will simply transcribe CIF data already held by NCDC into the study CRF. An analysis will then be performed to determine CRF completeness and any changes required.

Only NCDC staff who already have access to personally identifiable information (PII) associated with the CIFs will have access to that information during this pilot. Any PII in CIFs will not be transferred to study CRFs and pseudonymisation codes will be used to link CRFs with their respective CIFs. Those involved in the study who do not work within NCDC and who do not already have access privileges to the CIFs and associated PII will only work with pseudonymised data and study participant identifiers. A secure digital registry of study participant identifiers and their respective personal identifiers will be kept by NCDC.

## 1.2 Background Information

Human mpox (previously known as monkeypox) was first described in a 9-month-old boy in 1970 in the Democratic Republic of Congo (DRC). Nigeria reported its first two cases of mpox in 1971 and the third case in 1978, then there was a 38-year gap until September 2017, when a resurgence of mpox occurred in Nigeria. Over 120 laboratory-confirmed and probable cases were reported between 2017 and 2018 and the majority presented with classical features of febrile prodrome accompanied by progressive generalised skin rashes. However, there were also reports of cases with an absence of distinct febrile prodrome, predominant genital ulcers and mpox associated with HIV-infection. Many aspects of the clinical features and natural history of mpox in Nigeria are yet to be investigated.

The COVID-19 pandemic may have impacted mpox surveillance activities in 2020, but suspected and confirmed cases have continued to be identified and reported between 2019 and 2022. Additionally, confirmed cases with history of recent travel to Nigeria continued to be identified in UK and other countries between 2018 and 2022. It also became apparent in 2022 that clade II MPXV has evolved into two main sub-clades: IIa and IIb. Both sub-clades can be seen in West Africa, including Nigeria, and IIb MPXV was responsible for the unprecedented outbreaks seen outside Africa in 2022, outbreaks that mostly affected gay, bisexual and other men who have sex with men and were spread via human-to-human close-contact transmission, particularly during sex. Different lineages are now being identified within these subclades. For mpox caused by clade II MPXV, little is known about the influence of sub-clade type on clinical manifestations and routes and efficiency of transmission, particularly in African populations.

In order to develop a mechanistic understanding of disease processes in MPXV infection, such that risk factors for severe illness can be identified and treatments can be developed, it is necessary to understand pathogen characteristics associated with virulence, the replication dynamics and in-host evolution of the virus, the dynamics of the host immune response, the transmission dynamics, and clinical factors underlying individual susceptibility to infection and complications of di.

While not a study of a pharmaceutical or non-pharmaceutical intervention for mpox, this study may involve additional procedures (some minimally invasive), collection of personal data and additional follow up. Participation may require biological sampling that will not immediately benefit the respective participant. The Investigators are keen that this protocol generates data that are standardised and collected in such a way that they can be compared with those from similar studies that may be performed in other countries and outbreaks, with the possibility to pool anonymised data with those from other studies to increase the sample size and the strength of analyses.

This study forms part of a larger mpox research project that, in addition to characterising the disease, will explore the prevalence, epidemiology and transmission pathways, and societal implications and opportunities for public health interventions in Nigeria. There will be collaboration and - with relevant permissions obtained - harmonisation of data collection and data sharing between relevant studies within the project. Examples include collaborating with a study evaluating secondary attack rates, epidemiological features and human and animal risk factors for transmission in households of cases, and another study that will explore exposure risk and transmission in high-risk groups.

The protocol and supporting documents for this study are designed in such a way that they can be used alongside future intervention studies, if such studies are launched. For these

reasons, where samples are collected, we aim to fulfil the standards of consent required by Medicines for Human Use (Clinical Trials) Regulations 2004.

## **1.3 Source of this Protocol**

This document is based on the ISARIC-WHO Clinical Characterisation Protocol (CCP), which builds on a global consensus on observational research in emerging infections of public health interest. Since its launch in 2013, the ISARIC-WHO CCP has been revised, often at short notice and in response mode, to address important gaps in public health and clinical knowledge and support clinical trials in response to outbreaks and exposures of public health importance.

Significant experience has been gained in using the CCP (e.g., over 850,000 CRFs completed for COVID-19 globally), which has informed revisions and led to overall improvements to the source protocol. The ISARIC-WHO CCP has been used in the UK in 2022 to study hospitalised patients with mpox, including those receiving antiviral treatments. Furthermore, database structures already exist that are available for use for this study, including mpox-relevant fields (further fields can be added, as required). These database structures are maintained by the University of Oxford and adhere to CDASH standardisation.

The ISARIC-WHO CCP can be used to study different infectious diseases of public health concern, as well as chemical, biological and radiological exposures; however, this study protocol has been made mpox-specific, as agreed by the investigators in the Nigeria-UK research collaboration for mpox.

## **1.4 Primary Objectives**

For potential participants meeting the entry criteria, our primary objectives for mpox in Nigeria are to:

- Describe the clinical features of contemporary mpox virus infections
- Describe characteristics of mpox viruses causing human mpox infections in Nigeria, including features that may be associated with disease severity or transmission (such as genotypic or phenotypic changes in viruses detected that are known to alter transmission)
- Describe, where appropriate, the use of treatments, including supportive care, and novel mpox treatments if they are used as part of clinical care in Nigeria during the study period
- Observe virus replication, excretion and evolution within the host, identify any viral determinants of severity and transmission using molecular sequencing of MPXV genomes obtained from lesion swabs, respiratory tract, blood, and – where relevant and/or residual clinical samples are available - urine, stool/rectal swabs, CSF, and other relevant samples
- Where feasible, obtain suitable samples to enable subsequent analysis of host immune responses to infection and therapies over time, including innate and acquired immune responses and circulating levels of immune signalling molecules

## **1.5 Secondary Objectives**

Secondary objectives are to collect evidence to:

- Help facilitate effective triage and clinical management of people with mpox

- Help determine infectivity and appropriate infection control measures for mpox
- Inform the development of clinical guidance documents and offer clinical recommendations to policy-makers based on evidence obtained

### 1.5.1 Specific objectives of retrospective internal data pilot

These objectives are only for the retrospective data pilot and are complementary to the above objectives:

- Identify the barriers and enablers to collecting data for this study at participating sites
- Determine the ability of this study to collect data from hospitalised cases, healthcare facility attendees, and community cases (no healthcare facility attendance)
- Estimate likely completeness of data collection during the study
- Ensure essential data fields are identified and maintained in the study CRF
- Identify for removal any superfluous or infeasible data fields in the study CRF
- Develop, maintain and update a clinical mpox data module in the Surveillance Outbreak Response Management and Analysis System (SORMAS)
- Produce a preliminary, rapid analysis of clinical features of mpox using aggregated retrospective data from >200 cases of mpox that occurred in 2022; the clinical characterisation analysis of this cohort may be combined with, or run in parallel to, an epidemiological study of the same cohort

## 1.6 Structure of this document: stratified recruitment according to local resource.

The study will be conducted at multiple sites, including hospitals and healthcare centres, and includes recruitment and research activities in community settings. It is appreciated that settings may vary in terms of clinical infrastructure, resources, and capacity. Distinction is made to allow for a resource appropriate implementation of the protocol, and it is understood that data and/or specimen collection may be limited in certain settings. Observational analyses will be stratified according to available samples and data.

For each participant, a case report form (a web-based electronic “eCRF” or alternatively a paper CRF) will be completed.

Tier Zero is the least resource-intensive option. Each additional tier builds on the preceding one:

- **Tier Zero (Clinical data collection only)** – Clinical data, and data derived from samples containing MPXV collected for clinical reasons, including MPXV genome sequence where available, will be collected by the study. No additional biological samples will be obtained for research purposes. The minimum clinical data set will summarise the illness episode and outcome, with the option to collect additional detailed clinical data at frequent intervals, according to local resources/needs.
- **Tier One (Clinical data collection, and biological sampling at recruitment only)** – As for tier zero, but with a set of biological samples collected at the recruitment visit
- **Tier Two (Clinical data collection, and longitudinal biological sampling)** - Clinical research samples and data will be collected on day of recruitment (*R* - Day 1; ideally at initial presentation to a health care facility), longitudinal samples will be obtained during illness (*S*), and samples may be obtained during convalescence (*C*) (see section 3.6).

As an mpox outbreak progresses and more cases occur, it is anticipated that research priorities and the local resource availability may change. It is possible that, within a given research site, cases recruited later in an outbreak may be sampled at a lower intensity (see sampling priority order, table 1) and/or may be recruited to a lower tier of the study.

The initial internal pilot using retrospective data from NCDC CIFs will operate at Tier zero only (that is, clinical data collection without research biological sampling).

## 1.7 Entry Criteria

This study will enrol eligible people (children and adults including pregnant women) with suspected, probable or confirmed mpox, relevant to the study objectives, as specified below.

### 1.7.1 Inclusion criteria

*Case definitions are informed by NCDC case definitions for mpox but some may have been amended for the purposes of recruitment to this study*

- Confirmed case of mpox: a clinically compatible case where mpox infection has been confirmed by laboratory testing
- Probable case of mpox: a clinically compatible case with epidemiological linkage but where laboratory confirmation of infection could not be obtained
- Suspected case of classical mpox according to the extant NCDC case definition (current definition: a person with acute illness with fever  $>38.3^{\circ}\text{C}$ , intense headache, lymphadenopathy, back pain, myalgia, and intense asthenia followed one to three days later by a progressively developing rash often beginning on the face (most dense) then spreading elsewhere on the body, including soles of feet and palms of hand) *or* suspected non-classical / atypical mpox based on a clinician's assessment (e.g., absence of prodromal illness but mpox lesions are present, or mpox lesions with a more localised distribution, or predominantly genital/ano-rectal mpox lesions)

The recruitment of confirmed and probable cases is preferred over the recruitment of suspected cases; however, suspected cases may be recruited at the discretion and direction of the study's central coordinating team if real-time laboratory diagnosis is not possible or proves to be too slow to facilitate timely recruitment of participants. If suspected cases are recruited, subsequent analyses of data will recognise the important differences between confirmed, probable, and suspected cases and, accordingly, separate analyses of a single sub-cohort (e.g., confirmed cases only, suspected cases only) or combined sub-cohorts (e.g., confirmed and probable cases) will be performed when necessary. If suspected cases are recruited, data from those participants where mpox is subsequently and confidently excluded by laboratory testing may provide a useful control group and/or reveal common alternative diagnoses in suspected mpox cases, which could help refine case definitions and clinical diagnostic guidance. However, the primary purpose of this study is to clinically characterise confirmed cases of mpox. A recruited suspected case may later become a confirmed case, if laboratory testing is delayed; all sub-cohort analyses will use participants' final mpox status based on data available at their outcome assessments.

A participant in a related study, such as the household transmission study, who becomes a mpox case while participating will be invited to also participate in this study. There is no obligation for such an individual to participate in both studies.



### 1.7.2 Exclusion criteria

- Confirmed diagnosis of a pathogen unrelated to the objectives of this study and there is no indication or likelihood of co-infection with MPXV
- Mpox is not suspected clinically and there is no laboratory evidence of MPXV infection

## 2 Study Design

This is a prospective observational cohort study with data collection and biological sampling for public health and clinical research purposes. The scope of the study and the research aims and objectives were identified and agreed at a research workshop hosted by NCDC in Abuja in 2022.

### 2.1 Sample Size and locations

This is a descriptive study of a re-emerging infectious disease, with cases and outbreaks occurring in parts of Nigeria that may mean recruitment is challenging; therefore, the sample size is not prospectively determined (i.e. convenience sampling). Recruitment of participants will depend on the emergence/re-emergence and spread of mpox balanced by the resources available to the recruiting centres. The sample size will vary for each location but should be as large as feasible and preferably without limit – at least within the resources available – to capture as many clinical data as possible. Based on analysis of recent data from known outbreak sites in Nigeria, a recruitment target of 200 participants (range 150-250) should be achievable and be of sufficient size to be both informative and representative.

This protocol will be opened at sites with capacity and capability to recruit to any tier of study intensity. The study will hibernate in the absence of any relevant cases. The study will recruit participants for 18 months from the launch date. The study will be completed by March 2025, unless an extension to the study proves necessary and is granted.

The aim is to have two or more states within Nigeria take part in the study. Selection of suitable hospitals (two per state), Primary Healthcare Centres (PHCs), Site Investigators and Local Study Teams will be performed by the Study Investigators. Selection will consider factors including mpox case numbers (including historical mpox case numbers), available resources and research capabilities, security issues and accessibility. Where possible, geographically separate states will be selected to increase geographic coverage across Nigeria, but this will be dependent on other factors, particularly accessibility and security issues. The study will initially open in one state; after a short period (e.g., one month), study experience to date will be reviewed, any required adaptations made, and the study will be expanded to at least one other state.

The study will commence in Lagos state (Lagos University Teaching Hospital; Lagos State University Teaching Hospital). If this proves successful, the study will expand to Rivers State (University of Port Harcourt Teaching Hospital; Rivers State University Teaching Hospital). Imo State (Federal University Teaching Hospital, Owerri; Imo State University Teaching Hospital) and Ogun state (Olabisi Onabanjo University Teaching Hospital; Federal Medical Centre Abeokuta) are reserve study locations in case recruitment in Lagos or Rivers State proves insufficient or infeasible.

## **3 Methods**

### **3.1 Identification of Potential Participants**

Approval of the responsible ethics committees and institutional authority will be obtained before patients are recruited at any site.

In hospital, potential participants will be identified through hospital staff upon presentation at recruiting sites and through public health agencies. When resources limit the number of patients enrolled to less than the number of patients presenting, sites should establish procedures to minimize bias in the selection of participants.

In the community, potential participants will be identified by Community Health Officers and Disease Surveillance and Notification Officers (DSNOs) and the study team notified via the NCDC.

### **3.2 Approach to Potential Participants**

Identification of potential participants will be made by usual care teams or dedicated research staff after screening admission data or through information shared securely by NCDC with the study team.

Hospitalised cases will be approached by locally employed dedicated research staff or members of the usual care team. Any approach will first be discussed with the usual/direct care team.

In some circumstances potential participants will have been discharged home well or with moderate disease for self-care and/or isolation at home. Decision to discharge will be the responsibility of the usual care team.

Community-based cases will be approached by NCDC staff familiar with the study and trained in informed consent. The NCDC officer will accompany the Disease Surveillance Notification Officer (DSNO) when they visit the patient at home to discuss their positive mpox result and provide public health advice. This will be the opportunity to explain the study and offer participation.

After informed consent, a community-based participant will be asked to attend a research visit at a state hospital associated with the study. This visit will include physical examination by a study clinician, answering questions required to complete the case report form, blood sampling, and having a chest x-ray, where necessary. This visit will not require admission to a hospital bed and the participant will not have to pay (using their own money) for transport to/from the hospital or for any aspect of the hospital-based research visit.

If a community-based participant declines to attend the state hospital or visiting the state hospital is not feasible (e.g., it is too far from the participant's home), the participant will be asked to attend a Primary Healthcare Centre (PHC) associated with the study. Here the study procedures will be the same as for a participant attending a state hospital, except chest x-ray will not be possible and therefore a chest radiograph will not be obtained. This visit will not require admission to a PHC bed and the participant will not have to pay (using their own money) for transport to/from the PHC or for any aspect of the PHC-based research visit.

Should a community-based participant decline attendance at a PHC, or attendance at a PHC is not feasible, a short interview will be conducted at the same time in the patient's home to complete relevant sections of the case report form. Consent to participate will also allow the research team to access stored residual material from the samples (swabs, scabs, blood

samples) used to establish the mpox diagnosis and associated data for those samples (e.g., mpox virus PCR Ct value; mpox viral sequencing data). This is recruitment at tier zero (see below).

Schematics showing the pathways for confirmed case participants, and for suspected case participants (should recruitment of suspected cases take place) are shown in Appendix A.

### **3.2.1 Tier Zero: data collection only**

Tier Zero activity involves only data collection and requires collection of limited clinical data from the routine health record, public health case investigation form, and pathogen data derived from samples obtained and tested as part of routine clinical care.

The initial internal pilot study will only collate and analyse, retrospectively, pseudonymised data that have been recorded or generated as part of routine clinical care and public health investigations (e.g., microbiology results; data from the public health case investigation form) and will therefore not require individual consent. All participants recruited prospectively to the subsequent study will need to provide informed consent to participate, irrespective of the tier being followed.

### **3.2.2 Tier One: data collection, and biological sampling at recruitment**

Patients will only be considered for enrolment to Tier One, which includes research biological sampling at recruitment, if appropriate infection control and prevention measures are in place and can be maintained.

Clinical data will be collected as per Tier Zero, but in greater detail using additional sections of the case report form. Tier One participants will be made aware of this activity via the participant information sheets.

Samples taken early may be most useful for identification or evaluation of risk factors for disease progression at a clinically relevant decision point; therefore, it is desirable to begin sampling as early as possible during a patient's illness.

### **3.2.3 Tier Two: data collection and additional biological sampling**

Patients will be considered for enrolment to Tier Two, which includes longitudinal research biological sampling visits, if appropriate infection control and prevention measures are in place and can be maintained, and if sufficient resource is available for longitudinal sampling visits.

Clinical data will be collected as per Tier One, but with longitudinal biological sampling. Tier Two participants will be made aware of this activity via the participant information sheets.

Samples taken early may be most useful for identification or evaluation of risk factors for disease progression at a clinically relevant decision point; therefore, it is desirable to begin sampling as early as possible during a patient's illness.

### **3.2.4 Linkage to related study of household- and network-transmission**

If an individual with confirmed mpox provides consent to participate in this study, they will also be invited to participate in the separate but associated household study *Understanding the human, animal and environmental epidemiology of mpox transmission in Nigeria* (see separate protocol). There is no obligation to participate in this separate study and declining participation will not exclude the individual from participating in the clinical characterisation study. If interested in taking part in the associated study, the participant will be asked to provide consent for researchers from the associated study to

approach members of the participant's household, and their other close contacts, to offer them participation in the associated study.

### **3.3 Standard of Care**

Provision of care will vary by severity of illness (primary care versus secondary and tertiary care), by location, and by treating physician. It is not possible to define a single standard of care and therefore to define what samples will be taken as a part of medical management and when. The NCDC National Monkeypox Public Health Response guidance includes clinical management guidelines; these will be shared with all participating sites as part of site initiation/set-up.

Participants in this study may have samples taken in addition to those required for medical management. The results of routine bloods tests (e.g. full blood count, renal function and liver function tests) and clinically-indicated chest radiography performed through participation in the study may be of benefit to the individual participant and, when samples and a chest radiograph can be obtained and in real-time, these results will be shared with the patients' clinical team as soon as they are reported. The results of other tests performed subsequently on stored research samples are unlikely to benefit the health of the participants and therefore will not be shared. The study will not provide or pay for medical care or referrals to medical care for study participants; however, the study will pay for all clinical laboratory blood tests and chest radiography (if clinically indicated) performed as part of the study protocol. Reasonable travel expenses to attend study visits will also be paid.

### **3.4 Consent**

Informed consent is one of the founding principles of research ethics. Its intent is that human participants can enter research freely (voluntarily) with full information about what it means for them to take part, and that they give consent before they enter the research.

The study will use the National Health Research and Ethics Committee (NHREC) templates for informed consent. Consent to participate will be obtained from parents/guardians for children who are too young to provide consent themselves, according to national standards for consent.

A participant information sheet (PIS) will be provided prior to consent and, where necessary, it will be translated from English into commonly spoken languages and dialects. Age-appropriate PIS will be provided for children. For potential participants who are unable to read and/or write, the content of the PIS will be explained verbally by trained research staff; this, along with the informed consent process, will be witnessed by a healthcare professional independent to the study. All potential participants will have the opportunity to ask questions about the study prior to providing consent. Once provided, consent may be withdrawn at any time (see section 3.10). Declining participation in the study will not influence or impact the patient's clinical care or management of their case by Public Health authorities.

Where adult patients lack capacity to consent to this Clinical Study, an appropriate consultee will be approached by staff trained in consent procedures that protect the rights of the patient and adhere to the ethical principles within the Declaration of Helsinki. Staff will explain the details of the study to the consultee and allow them time to discuss and ask questions. The staff will review the informed consent form with the person giving advice and endeavour to ensure understanding of the contents, including study procedures, risks, benefits, the right to withdraw and alternatives to participation.

In some situations, the appropriate consultee, parent, or guardian may be confined to a remote location under conditions of quarantine or self-isolation. In these circumstances'

consent/consultee advice will be sought by telephone or voice-over-internet communication using a telephone-witnessed consent/consultee declaration form.

At sites working within a paperless environment (e.g., for infection prevention and control purposes) electronic consent is permitted only with prior agreement from the central coordinating team for the study. Electronic consent systems, if used, must exactly mirror the content of the Research Ethics Committee-approved consent forms for this study.

Participants who agree to participate (or their parent/guardian or consultee who declares their wishes to do so) will be asked to sign and date an informed consent form or consultee declaration form. Summary information sheets and consent forms have been produced to reduce the initial burden on patients, parents/guardians and consultees and these summary information sheets will be used as the basis for the consent discussion. The full study information sheets for adult patients, parents/guardians, and consultees will be provided for their information, after the initial consent discussion.

In the case of adult participants who are unable to give informed consent due to mental or physical status, the wishes of the participant may be declared by an appropriate consultee according to the site policy on obtaining consent for medical procedures. If, during the course of the study, the participant's status changes such that they are able to consider consent independently, informed consent must be discussed and obtained.

Parents or guardians of children under the age of 12 years old will give consent for their child. Study staff obtaining consent will consider the ability of the child to understand the principles of the study and will discuss the study with the child in age appropriate language. Where appropriate, children will be invited to give assent, which will be recorded on the informed consent form. Children aged 12-18 years will provide assent and their parents/guardian will provide consent. The right to withdraw at any time without negative impact will be reinforced with the child and their parent/guardian. Should the Nigerian rules on consent by young people for research purposes alter during the period of this study to allow consent by competent minors, then these new rules will be applied to this study without further amendment.

A contemporary record should be made in the clinical notes that this information has been shared with the parent(s) or person(s) with parental authority.

In view of the importance of early samples, participants or their parent/guardian/consultee will be permitted to consent/give advice and begin to participate in the study immediately if they wish to do so. Those who prefer more time to consider participation will be approached again after an agreed time, normally one day, to discuss further.

Participation in the study will not influence the medical treatment offered to patients and declining participation will not deny patients care or treatment that they otherwise would have received. Participation in this study may provide a participant with the opportunity to have additional clinically-useful tests performed, the results of which will be shared with the participant's clinician(s); examples include routine bloods tests and chest radiography performed as part of the study sampling/investigation schedule.

For activity that requires use of patient derived biological material consent forms will be provided in plain English. Illiterate participants will have the consent form read in the presence of a witness, who will sign to verify the accurate reading of the form and agreement of the participant. For participants who cannot understand the language of the available forms, verified translations will be made when possible. If it is not possible to prepare a translation in a required language, verbal translation of the document and the consent

discussion (if required) will be used. In this case, the translator may act as the witness for consent and sign the consent form so that patients who cannot read the language of the forms are not excluded from this research.

An mpox outbreak is a public health incident and between May 2022 and May 2023, mpox was a Public Health Emergency of International Concern (PHEIC), as declared by the WHO Director General. For patients who are incapable of giving consent in emergency situations the process of consent will comply with Nigerian guidelines on informed consent for research. These are exceptions clearly acknowledged in the Declaration of Helsinki (2008), and the following process will be observed:

- All efforts will be made to have consent from appropriate consultee /guardian/carer when available, and from the patient at the earliest opportunity.
- If a patient is incapable of giving consent and there is no relative/representative present, two doctors (one independent of the study team with knowledge of the patient condition) will consider the patient's eligibility criteria and any known views of the patient about his/her participation. Together they will decide whether or not is appropriate to enrol the patient in the study.

Participants will be invited to participate in a convalescent sampling visit if their respective study sites have sufficient capacity to conduct these visits.

Participants in this study will also be asked to give permission for the research team to make contact to discuss participation in an epidemiological study focussed on exposure and transmission among household and network contacts, which is a component of the Nigeria Mpox research project and which will be implemented contemporaneously with the clinical study.

A copy of the informed consent form will be given to the person who gives consent, and a copy will be sent securely to the central study team for monitoring of informed consent and study administration. For those consenting via telephone a copy of the completed telephone consent form should be given to the participant at the earliest opportunity. In cases of electronic consent, the completed e-consent form should be given to the participant.

If the version of a consent form is updated after a participant gives their consent for participation, and that participant is returning for follow-up visits or further sample collection, every effort should be made for them to re-consent on the new version. There is no expectation that participants **not** remaining as hospital inpatients or returning for follow-up visits be contacted to re-consent.

Potential participants identified by residual diagnostic materials that present an important research opportunity will be contacted to consent to the use of their pre-existing samples for this study and future research. This may involve an information sheet and consent form being posted to the potential participant by their usual clinical team, with a pre-paid envelope for return, or a telephone call to the individual asking if they are interested in participating. The approach for consent could also take place in person if the potential participant remains in hospital.

If the potential participant is in hospital, local translation services may be used for patients who do not understand English, or the information sheet may be read to the patient, with consent appropriately witnessed, for illiterate patients.

For potential patients being asked to consent from home, a phone call or video call (e.g., WhatsApp or Zoom) may be used to explain the study and obtain informed consent, with

communication in the relevant language or dialect where indicated. Any virtual consent process will always be witnessed by another appropriate professional.

If the potential participant is known to have lost capacity to consent since being discharged from hospital, the direct care (clinical) team will identify the next of kin from the patient medical records to ascertain whether they can act as a consultee. If no suitable consultee is identified, potential patients without capacity who have already been discharged from hospital will not be contacted to provide consent.

This study will not seek to collect data or biological samples from patients who are deceased and did not consent to participation prior to death.

### **3.5 Sampling of Participants**

Prospective sampling of people for research purposes must only be done after gaining consent or assent. After consent is obtained, residual samples may be used for research and development.

Samples required for medical management will always have priority over samples taken for research tests. Obtaining aliquots of residual clinical sample material or sampling for research purposes should never compromise the quality or quantity of samples required for the patient's medical management. Wherever practical, taking research samples should be timed to coincide with sampling for clinical purposes. The research team will be responsible for sharing the sampling protocol with healthcare workers supporting patient management, to minimise disruption to routine care and avoid unnecessary procedures.

Some samples must be processed according to the Study's Laboratory Manual. The Laboratory Manual may change over time, due to the nature of the pathogen of interest and as national guidance is developed.

### **3.6 Sampling, Investigation, and Data Collection Schedules**

Tier of activity for sampling will reflect local recruitment and laboratory capacity and the operational circumstances for an mpox outbreak. It will also reflect the location of the patient (community-based versus hospitalised) and, for community-based participants, the participant's willingness to attend research visits at a study-associated hospital or PHC, and the feasibility of attending a study associated hospital or PHC.

There is deliberate flexibility in the biological sampling schedule (see Table 1, below) to reflect operational challenges in the field, including in community settings, and potential variability in available sampling resources at different sites/locations. The same sampling schedule applies to both hospitalised and non-hospitalised participants and, where possible, all scheduled sampling visits should be completed. Where it is not possible to complete all sampling visits, this will not result in a protocol violation, but the reason for a sampling visit being omitted must be recorded. When there are resource limitations that prevent all sampling visits being completed, sampling visits should be completed according to the priority order stated in Table 1.

The recommended longitudinal sampling schedule for Tier Two participants aims to capture a number of timepoints during acute illness when changes in viral dynamics and the immunological response to mpox can be expected to occur. The schedule is also designed to obtain later samples when it is reasonable to expect recovery or resolution to occur, or identify persistence of infection in some individuals (e.g., those with immunosuppression). This schedule has been informed, in part, based on smaller studies of clade II mpox done in other countries, including in the UK. Similarly, the priority order for when sampling at all

recommended time points is not possible (see Table 1) aims to focus on obtaining 1-3 samples from acute illness (one from each of recruitment, week 1, and week 2), as it is believed these will be the most useful samples for subsequent laboratory analyses, and are more likely to be obtainable than a convalescent sample. Obtaining more than one sample set in each of weeks 1 and 2 is of the least value and hence these have the lowest priority (below obtaining a convalescent sample).

The schedules below may be modified, depending on the circumstances of a particular mpox outbreak or event, by omitting some samples to conserve resources. This will be achieved by providing sites with a specific modified schedule, in the format below but with some elements removed. Since this would in all cases result in a reduced burden to patients and recruiting sites, no explicit ethical or management approval will be sought for these omissions.

	<b>Recruitment</b> (hospital cases and, if feasible, community cases)	<b>Week 1</b> (hospital cases and, if feasible, community cases)							<b>Week 2</b> (only if hospital case remains admitted, or a case is accessible in the community)							<b>Convalescent sample</b>
Day	1	2	3	4	5	6	7	8	9	10	11	12	13	14	Between days 28 and 56	
Sample set	R		S		S				S					S	C	
Priority	1		2		5				3					6	4	

**Table 1. Sampling schedule** If local resource limitations require sampling frequency to decrease, samples will be prioritised as shown (1=highest priority). Sample sets refer to the tables below: R – Recruitment samples; S- Serial samples; C – convalescent samples. For Tier 1 samples are collected at recruitment only. For tier 2, serial samples and convalescent samples are collected in addition to samples collected at recruitment.

The sample sets described in Table 2 (below) may be modified, depending on the circumstances of a particular mpox outbreak or event, by omitting some samples to conserve resources. This will be achieved by providing sites with a specific modified schedule, in the format below but with some elements removed. Since this would in all cases result in a reduced burden to patients and recruiting sites, no explicit ethical or management approval will be sought for these omissions.

Maximum blood volumes drawn for research purposes and the suggested distribution of those volumes between different types of blood collection tube are described in Table 3, below.

A summary of the sampling and documentation required at recruitment (all participants), serial sampling visits (if tier 2), date of hospital discharge (if hospitalised), and convalescent sampling visit (if tier 2) are described in Table 4, below.

Where a hospitalised participant is otherwise medically fit for discharge and symptoms have resolved but the patient remains an in-patient for other reasons, the convalescent sample (if tier 2) should be taken at day 28 after mpox illness resolution or shortly thereafter.



### 3.6.1 TIER ZERO schedule – Clinical data only

Clinical data are collected and entered into the CRF, including the results of any laboratory testing performed for clinical reasons e.g., mpox diagnostic result, mpox virus Ct value, and HIV antibody result from Public Health/clinical records. Consent is also provided to access residual material and data (e.g., sequencing data) associated with these samples, for the purposes of research analyses performed within this study.

### 3.6.2 TIER ONE schedule – Clinical data collection, and sampling at recruitment only

In addition to collecting clinical data, a single research sample set is obtained at recruitment (R), or as soon as practical following recruitment.

Blood sample volumes will be limited by the estimated weight of the patient. In the absence of a measured weight, people aged 18 years and over may generally be assumed to be over 40kg unless there is other clinical concern.

#### 3.6.2.1 Baseline chest radiograph

Hospitalised cases, and community cases who are able to attend a research visit at a state hospital, will have baseline chest radiography if it is clinically indicated (that is, where the attending clinician believes a chest radiograph will help inform diagnosis and clinical management). The cost of the procedure and reporting will be met by the study, not by the participant, unless a chest radiograph has already been obtained prior to recruitment to the study. The chest radiograph and any associated radiology reports will be shared with the participant's clinician as soon as they become available.

### 3.6.3 TIER 2 schedule – Clinical data collection with serial biological sampling

In addition to data, recruitment samples (R), and baseline chest radiograph (if applicable) collected at recruitment as per Tier 1, acute serial sample sets (S) and one convalescent set (C) are obtained if a patient is recruited at Tier 2. The Tier 2 schedule will be followed where appropriate resources are available and make it feasible. Residual material from clinical care, including diagnostic samples, excised tissue/organs, and other materials, may be retained for research purposes, and specific samples will be collected according to the schedule below

*Table 2. Tier 1 and Tier 2 research sample set – to be obtained at each sampling point. This may be revised in response to specific conditions as some samples will not be necessary or useful.*

Research sample type	Processing/ storage	Purpose
Blood sample in EDTA tube(s) Blood sample in serum separator tube(s) Blood sample in fluoride oxalate tube Blood culture - only if evidence of sepsis	Immediate testing in clinical laboratory on site, or send immediately to the nearest study-associated clinical laboratory for testing	Full blood count, renal profile, liver profile, bone profile, blood glucose, HIV serology, CD4 count (if HIV test is positive)

Pathogen samples: <ul style="list-style-type: none"> <li>Throat swab sample in viral transport medium</li> <li>Urine (up to 10ml), do not fill the container.</li> <li>Stool (up to 10ml) if produced;</li> <li>Mpox swab samples (minimum of two, maximum of four) in virus transport medium from mpox lesions and infected sites/vesicles/ulcers/sores/mucosa</li> <li>Shed mpox lesion scabs if produced</li> <li>Also store any residual volumes from samples taken for clinical care e.g. CSF</li> </ul>	Do not process at site. Keep doublebagged. Store at -80°C*	Pathogen studies to reveal changes in pathogen during infection and during spread between individuals, detect development of resistance.
Oral fluid (Crevicular fluid)	Do not process at site. Keep doublebagged. Store at -80°C*	Non-invasive determination of humoral immune response
Blood sample in serum (clotted) tube(s)	Serum supernatant (3 aliquots -80°C*)	Mediators/biomarkers
		Serology
Blood sample in EDTA tube(s)	Plasma supernatant (3 aliquots -80°C*)	Mediators/metabolites/biomarkers
		Detect RNA/DNA from pathogens.
	Cell fraction (1 aliquot -80°C*)	RNA/DNA from pathogens.

\*freeze at -80°C where possible, or at least at -20°C. If necessary (eg. weekends/public holidays) store in refrigerator until processing. For details, see Laboratory Manual.

Table 3. Maximum blood volumes by weight – applicable to Tier 1 and Tier 2

	Blood samples at visit	Total volume of blood
>40kg	<b>3ml</b> EDTA blood for FBC <b>3ml</b> blood in serum separator tube for biochemistry <b>2ml</b> blood in fluoride oxalate tube for glucose <b>3ml</b> blood in blood culture tubes (only if sepsis) <b>3ml</b> clotted blood in plain tube <b>3ml</b> blood in EDTA tube <b>1ml</b> blood in EDTA tube	Maximum any day: 18.5ml (0.46ml/kg) Maximum any 4 weeks (applies to tier 2 only): 96ml (max 2.4ml/kg)
20 to 40kg	<b>3ml</b> EDTA blood for FBC <b>3ml</b> blood in serum separator tube for biochemistry <b>2ml</b> blood in fluoride oxalate tube for glucose <b>3ml</b> blood in blood culture tubes (only if sepsis) <b>3ml</b> clotted blood in plain tube <b>1ml</b> blood in in EDTA tube	Maximum any day: 15ml (0.6ml/kg) Maximum any 4 weeks (applies to tier 2 only): 42ml (max 2.1ml/kg)

10 to 20kg	<b>1ml</b> EDTA blood for FBC <b>1ml</b> blood in serum separator tube for biochemistry <b>1ml</b> blood in fluoride oxalate tube for glucose <b>3ml</b> blood in blood culture tubes (only if sepsis) <b>1ml</b> clotted blood in plain tube <b>1ml</b> blood in in EDTA tube	Maximum any day: 8ml (0.6ml/kg) Maximum any 4 weeks (applies to tier 2 only): 23.6ml (max 2.36ml/kg)
4 to 10kg	<b>1ml</b> EDTA blood for FBC <b>0.5ml</b> blood in serum separator tube for biochemistry <b>0.5ml</b> blood in fluoride oxalate tube for glucose <b>0.5ml</b> blood in EDTA tube	Maximum any day: 2.5ml (0.5ml/kg) Maximum any 4 weeks (applies to tier 2 only): 9.4ml (max 2.35ml/kg)
< 4kg	<b>0.5ml</b> EDTA blood for FBC <b>0.5ml</b> blood in serum separator tube for biochemistry	Maximum any day: 1.1ml (~0.27ml/kg) Maximum any 4 weeks (applies to tier 2 only): 4.4ml (max 2.4ml/kg)

Blood sample volumes will be limited by the estimated weight of the patient. In the absence of a measured weight, people age 18 years and over may generally be assumed to be over 40kg unless there is other clinical concern.

*Table 4. Sample collection and documentation requirements for different visits/events*

	Samples/documents
<b>R – RECRUITMENT SAMPLE SET</b> (applies to tier 1 and tier 2)	Consent form OBTAIN SAMPLE SET Initiate STUDY CASE REPORT FORM (CRF) Complete ADMISSION and DAILY FORM in the CRF
<b>S- SERIAL SAMPLE SET</b> (applies to tier 2 only)	OBTAIN SAMPLE SET Complete another DAILY FORM in the CRF
<b>On hospital discharge (if hospitalised)</b>	Complete OUTCOME FORM in the CRF Plan Convalescent Visit and, if applicable, coordinate with the separate household transmission study to plan the convalescent visits for household participants in that study
<b>C – CONVALESCENT SAMPLE SET</b> (applies to tier 2 only)	OBTAIN SAMPLE SET Update OUTCOME FORM in CRF

### 3.6.4 Convalescent Sampling

There is a need for additional sampling after recovery from acute illness to enable generation of serological tests, setting of reference standards for serology, potential extraction and culture of PBMCs for cellular immunology studies, and generation of monoclonal antibodies

for research, diagnostic and therapeutic use. These studies are often extremely valuable in the global response to an emerging or re-emerging infectious disease.

Serum will be separated and stored, for serological studies and other serum-dependent analyses. Depending on available laboratory resources, immune cells, including monocytes, monocyte-derived macrophages, neutrophils and lymphocytes may be isolated from peripheral blood and studied immediately or following cell culture. Gene expression, protein synthesis and degradation, cytokine release and other functional studies may be measured. Cells may be stored for future use and may be used in the generation of commercial products.

Patients who participate in convalescent sampling may be invited to provide additional samples under separate consent for this part of the study. Participants will be fully recovered with no contraindications to blood donation, including:

- Infection with any blood borne diseases (e.g. HIV, Hepatitis B or Hepatitis C)
- Previous or current intravenous drug abuse
- Current anaemia
- Blood clotting disorders
- Current anticoagulant (blood thinning) drug therapy
- History of donations to a blood transfusion service (or any other donation, such as a bone marrow donation) within the last 12 weeks.

Depending on the participant's weight, the following maximum volumes of blood will be obtained:

- >40kg: 240mls (6.0mls/kg)
- 20-40kg: calculated<sup>3</sup> at 2.4ml/kg
- <20kg: calculated at 2.4ml/kg

The actual total volume of blood drawn at the convalescent sampling visit may be less than the maximum volumes stated above, but will not exceed those stated maximums.

### **3.7 Enrolment Procedures for Patients**

Patients who meet the inclusion criteria and who have given informed consent to participate directly, or have been consented by a parent/guardian or whose wishes have been declared by a consultee, or be it deferred, proxy or assent, will be enrolled to the study. With due consideration to the circumstances of admission to a healthcare facility (if applicable), a summary information sheet will be used as the basis of the consent discussion and a full study information sheet will be given subsequent to the consent discussion.

All hospitalised patients will have clinical information collected either directly through examination including a review of medical, contact and travel history, or from available medical notes when this is not possible. Information will be recorded in the case report form.

At the recruitment visit, hospital and Primary Healthcare Centre (PHC) sites with available resources will obtain a research sample set (see section 3.6).

Community-based participants will be enrolled in the community, typically their own homes. Following consent, a community-based participant will be asked to attend a research visit at a state hospital associated with the study. This visit will include physical examination by a

study clinician, answering questions required to complete the case report form, blood sampling, and having a chest x-ray, when indicated. This visit will not require admission to a hospital bed and the participant will not have to pay (using their own money) for transport to/from the hospital or for any aspect of the hospital-based research visit.

If a community-based participant declines to attend the state hospital or visiting the state hospital is not feasible (e.g., it is too far from the patient's home), the participant will be asked to attend a Primary Healthcare Centre (PHC) associated with the study. Here the study procedures will be the same as for a participant attending a state hospital, except chest x-ray will not be possible and therefore a chest radiograph will not be obtained. This visit will not require admission to a PHC bed and the participant will not have to pay (using their own money) for transport to/from the PHC or for any aspect of the PHC-based research visit.

Should a community-based participant decline attendance at a PHC, or attendance at a PHC is not feasible, a short interview will be conducted at the same time in the patient's home to complete sections of the case report form. Consent to participate will also allow the research team to access stored residual material from the samples (swabs, scabs, blood samples) used to establish the mpox diagnosis and associated data for those samples (e.g., mpox virus PCR Ct value; mpox viral sequencing data). This is recruitment at tier zero (see below).

The day of initial sample collection will be counted as Day 1. All study days will be counted from this point forward. Clinical information will also be collected on discharge.

For the internal pilot study using collation of retrospective data from Public Health case investigation forms, only pseudonymised data will be collected and analysed.

### **3.8 Case Report Form and Participant Numbers**

Case Report Forms (CRFs) will be used to collect data at enrolment to this study. Electronic CRFs (eCRFs) are preferred and will be used where feasible, although some sites with resource limitations may require completion of paper CRFs.

Participant numbers consist of a centrally assigned 5-character digit site code and a locally assigned 4-digit patient number. Local investigators should be assigned patient numbers sequentially for each site beginning with 0001. In the case of a single site, recruiting patients on different wards, or where it is otherwise difficult to assign sequential numbers, it is acceptable to assign numbers in blocks; e.g., Outpatient ward will assign numbers from 0001 onwards and In-patient ward will assign numbers from 5001 onwards. If a paper CRF is used, the patient identification code will be entered at the top of each and every sheet. For settings or circumstances in which resources are constrained, an abbreviated core case report form may be provided (a 'core CRF').

For the internal pilot study, existing pseudonymised data from Public Health Case Investigation Forms into the study CRFs.

The eCRF will be made available by registering on the study's data management system.

### **3.9 Follow-Up Procedures for Patients**

Follow-up procedures will be undertaken only when resources allow, according to tier 2 sampling outlined in Table 1. Follow-up procedures will only be undertaken if appropriate biological safety measures can be maintained. Sites unable to perform daily follow-up as

described below may reduce the frequency of follow-up procedures or exclude follow-up if necessary.

Regular clinical assessment and sampling will follow local guidelines. All patients will have further clinical information recorded in the case report form to record events and treatment experienced during hospitalization, and the outcome of the illness episode. Some of the samples described below will coincide with clinical management. The number of these will depend on the applicable care guidelines, the treating physician and the health of the patient.

For the purposes of this study, clinical resolution of acute mpox illness is defined as cessation of the appearance of new skin and/or mucosal lesions and all existing lesions have healed (no vesicles, no pustules, no ulcerating tissue; granulation tissue and scabs may be visible on some lesions). Time to virological resolution of acute mpox illness (MPXV can no longer be detected in appropriate samples) is not an outcome being assessed in this study, but virological trajectories will be monitored in some participants where feasible e.g., decreasing viral load or viral load surrogate in serial samples of the same type.

Follow-up procedures may include contact by writing, telephone, SMS and contemporary digital communications media, as stated in the PIS. These may lead to interviews or further biological sampling (using sample sets included in main protocol or relevant sub- study to which the participant will have consented). Withdrawal of Participants

Any patient who is a suspected or probable mpox case (not a confirmed case) *at the time of enrolment* and whose illness is *subsequently* confirmed to be the result of an infection other than mpox, and who has no indication or likelihood of co-infection with mpox, will end the study at that point. No further follow-up will be conducted, but data will be retained to provide control-comparison data and improve understanding of alternative diagnoses that may be mistaken for mpox. Samples collected will be retained unless the participant requests they be destroyed.

Patient autonomy to withdraw from sampling at Tiers 1 and 2 of study at any time must be respected, and residual samples will be destroyed.

## **4 Specimens and Laboratory Analysis**

### **4.1 Specimen Sampling, Storage Procedures and Transport**

Appropriate selection and timely collection of high-quality specimens, proper storage procedures and comprehensive diagnostic testing will ensure the quality of data.

Care must be exercised to ensure the safety of hospital staff and other patients. Strict adherence to collection protocols, biosafety and adequate personal protective equipment (PPE) is essential.

Sites should follow the usual sources of advice regarding laboratory containment of the pathogen. In an emerging infection this may include information from national organisations, such as NCDC, that would support a local risk assessment and SOP covering the handling of samples from the affected patient.

Site laboratories planning to participate in the study must consider how they would fulfil a requirement to handle research samples in addition to clinical samples.

All samples collected must be labelled as per hospital procedure with appropriate pseudonymised patient study codes and hazard labelling according to local policy and ideally marked with a freeze-proof research label or with a solvent resistant marker. Samples

collected in the household will be labelled with pseudonymised patient study codes. Samples will be processed as per the table below. Samples that cannot be analysed in Nigeria may be exported to an associated laboratory in another country for testing, as long as specific permission of the patient/parent/guardian/consultee was obtained at enrollment. Any samples sent to external research laboratories outside Nigeria will be pseudonymised with unique coded identifiers to protect the identity of the patient at the site level at the point of enrolment. When required, national guidance will be adhered to for the transport of specimens.

Clinical samples will be labelled with standard hospital information, including the sample date and sent with the standard lab request forms.

Research samples for participants will be sent to the associated NCDC laboratories in Nigeria. The study team will organise couriers.

Patient numbers should be assigned sequentially by each site beginning with 0001. In the case of a single site recruiting patients on different wards, or where it is otherwise difficult to assign sequential numbers, it is acceptable to assign numbers in blocks. E.g. Outpatient ward will assign numbers from 0001 onwards. In-patient ward will assign numbers from 5001 onwards. The patient identification code will be entered at the top of each and every CRF sheet. Patient numbers and identifiers will be shared with NCDC. Patient identifiers will not be shared with research institutes.

A unique alphanumeric code for patient samples will be given to each participant and the only link between the patient's identifying data and this code will be held securely and shared only with the study administrators. The study administrators will link patient data numbers with sample identifiers. The patient identifiers will be shared with NCDC staff for purposes of cross-linkage to the participant's Public Health case investigation form, and, if consent to participate in the household study is provided, with the household study recruiting team; otherwise, patient identifiers will not be shared with any party.

Residual volumes available after clinical and research testing is complete will be retained for future ethically approved research and this may include commercial purposes.

## 4.2 Sample Processing

### 4.2.1 Tier 1 sample processing

No processing of research-only samples is required at site. Samples will be shipped to the designated study laboratory for further processing and distribution. Blood samples for immediate haematology, biochemistry, microbiology and virology testing will be tested in the site's clinical laboratory, or the nearest clinical laboratory associated with that site.

### 4.2.2 Tier 2 sample processing

Table 9. Initial sample processing

Sample	Initial processing	Aliquots	Initial transfer	Research purpose	Laboratory doing analyses
Blood samples (clotted)	Centrifuge 1500g for 10mins.	Supernatant: freeze at -80°C*	Study-Associated Laboratory	Serology	NRL
		Supernatant: freeze at -80°C*		Circulating mediators by multiplex cytokine/chemokine assays and proteomics	TBC
		Supernatant: freeze at -80°C*		Mediators/proteomics other assays	TBC
Blood samples (EDTA)	Centrifuge 1500g for 10mins ideally at 4°C.	Supernatant: freeze at -80°C*		Serology	NRL
		Supernatant: freeze at -80°C*		Circulating mediators by multiplex cytokine/chemokine assays	TBC
		Supernatant: freeze at -80°C*		Other studies if relevant (eg pharmacokinetics/ pharmacodynamics)	TBC
		Cell pellet: freeze at -80°C*		High-throughput genotyping and/or high coverage genome sequencing	TBC
Share of CSF (if obtained for clinical purposes)	Freeze at -80°C*	Aliquot if safe to do so into 3 aliquots Freeze at -80°C*		Pathogen detection, quantification, viral genome sequencing and isolation	NRL
				Serology	NRL
Pathogen samples (e.g. swabs & scabs)	Do not process	Freeze at -80 °C*			Pathogen detection, quantification and viral genome sequencing and isolation.

\*freeze at -80°C where possible, or at least at -20°C. If necessary (eg. weekends/public holidays) store in refrigerator until processing is possible. NRL = National Reference Laboratory. TBC = To be confirmed

Sample processing should follow the Study's Laboratory Manual.



## 4.3 Use of Stored Samples

Access to samples for additional analyses will be governed by a Data and Materials Access Committee. This Committee will include the Chief Investigator for this study, the senior co-leads (Nigeria and UK) for the overall mpox project, and additional scientific advisers/assessors as determined necessary by the Chief Investigator. Linked, pseudonymised data generated during the course of these studies may be shared between investigators within the overall mpox project. Each local site will hold their own data.

Where possible and within the constraints of international law and specific requirements of local ethical and institutional management approvals, pseudonymised clinical data will be shared centrally within one master database held in Nigeria which will be fully compliant with standard data management processes and local regulations. This database will be held on servers. Access to data for outside investigators will be reviewed by the independent data and materials access committee.

Samples will only be stored in containment facilities that have appropriate biological safety measures in place and have received necessary authorisation to store samples (according to national regulations for mpox samples).

### 4.3.1 Research Plan for samples

The laboratory component of the study is focused on capacity strengthening in the country. All laboratory components feed directly into the research objectives of the studies and are not considered separately from the study aims itself.

This document is a standardized protocol for the rapid, coordinated clinical investigation of mpox. The protocol is designed to have some level of flexibility in order to ensure the broadest acceptance and has been initiated in response to recurrent outbreaks of mpox in Nigeria and elsewhere. This protocol is based on the ISARIC Clinical Characterisation Protocol, which has been designed to maximize the likelihood that data and biological samples are prospectively and systematically collected and shared rapidly in a format that can be easily aggregated, tabulated and analysed across many different settings globally.

A high-level overview of expected analyses using the samples collected is given here. No such plan can be predictive of future research questions and priorities; however, specific research questions, hypotheses, and experimental designs are being developed for intended research laboratory analyses that will use samples collected during this study. These will reflect research priorities agreed by the investigators and collaborators, as well as considering available resources and feasibility assessments.

Is it not guaranteed that all proposed laboratory analyses will take place, either as part of this study or through collaboration and sharing of data and samples (with appropriate consent and approvals) with other researchers. Investigators will meet to plan any such work before it commences. Samples may be used for commercial purposes, with appropriate consent.

#### **Characterising the biological features of mpox**

1. Descriptive analysis of common clinical haematology and biochemistry variables, including inflammatory markers and markers of end-organ abnormalities, in patients in the acute phase of mpox and, where longitudinal samples are available, analysis of changes in common haematology and biochemistry variables during the course of illness

#### **Host response to infection**

1. Quantification of multiple soluble immune mediators (cytokines and chemokines) in blood and blood-markers using high-sensitivity assays, including comparisons of levels in longitudinally obtained samples, to better understand the nature of the innate and adaptive responses to MPXV infection and how these may be associated with disease manifestations and outcomes.
2. The production of anti-orthopox antibodies in response to natural infection over time and how these relate to differences in clinical courses and viral replication dynamics in infected individuals. This will use a UK-developed and validated anti-orthopox ELISA antibody assay, with transfer of the technology to the NCDC and study laboratories in Nigeria.

### **Host susceptibility to infection and complications of infection**

1. Quantification of anti-orthopox antibodies at baseline (recruitment) and how these relate to the subsequent, observed clinical course of mpox and the viral dynamics in the infected individuals.
2. Identification of HIV-associated immunosuppression and how this affects course of illness, occurrence of complications, and clinical outcomes.

### **Viral dynamics and virus characteristics**

1. Quantification of MPXV present in different samples using quantitative/semi-quantitative PCR and, where longitudinal samples are obtained, how these change over time and how the dynamics relate to the observed clinical course, severity of mpox and clinical outcomes. This will use a UK-developed and validated MPXV-specific qPCR assay, with transfer of the technology to the NCDC laboratories in Nigeria.
2. Genetic sequencing of lesion-swab samples and blood samples containing viral DNA to look for within-host genetic changes in MPXV over time, whether this is influenced by non-viral factors such as host immunodeficiency states (e.g. severe immunosuppression) and/or drug-selection pressure (should anti-orthopox antivirals be administered), and how any viral genetic changes detected relate to the observed course of disease.
3. Comparison of sequences obtained from two different anatomical sites within an individual to see if these differ and whether they are associated with different patterns or severities of mpox disease at those different anatomical sites.

Any use may include or lead to commercial development of diagnostic and therapeutic products and processes.

## **4.4 Future Use of Samples**

All use of data and samples will be controlled by the Data and Materials Access Committee.

Samples collected will be used for the purpose of this study as stated in the protocol and also stored for future use. The standard consent form will request consent from subjects for sample storage and/or export of specific samples to collaborating institutions for investigations, including commercial use.

Any proposed plans to use samples other than for those investigations detailed in this protocol will be submitted to the relevant ethics committees prior to any testing. Collaborating centres must have appropriate biological safety measures and regulatory approvals in place in order to receive samples.

Future use may include commercial development of diagnostic and therapeutic products and processes, preferably within Nigeria.

Any database detailing clinical data will only identify participants by a participant number. Participant names or any other identifying details will NOT be included. Data may be used alone or in combination with data from related studies in secondary analyses. The database containing personal identifiers and patient number (i.e. the key) will be held securely and encrypted by NCDC on a NCDC-owned server in a digitally distant location unlinked to that containing the clinical data and research data.

## **5 Medical Management and Safety Reporting**

### **5.1 Medical Management**

Medical management will be according to standard of care at the treating site and not a part of this research protocol. Research interventions include only collection of clinical information, biological specimens and a baseline chest radiograph; therefore adverse event reporting is not applicable, as there is no intervention. Results of any clinically-relevant tests performed, including hematology and biochemistry blood tests, and a baseline chest radiograph, will be shared with the participant's clinician(s) (if applicable), as soon as they are available. The research team is not responsible for acting on these results or providing medical care, only for sharing the results with the participant's clinician(s) in real time.

## **6 Data Management**

### **6.1 Data Collection**

Clinical and laboratory data will be collected during the acute illness period according to local resource availability. Priority at all times will be given to the collection of clinical information. Research data will be integrated as much as possible with information available from healthcare and Public Health records. Clinical data will be collected locally within a study CRF relevant to mpox. The data will be pseudonymised at site and a study number issued.

The patient's hospital number or other healthcare identifier, date of birth and postcode will be recorded at the site for data linkage. The participant's telephone number will be recorded at time of consent so they can be contacted to arrange convalescent sampling (if Tier Two) and invited to participate in future studies or to provide SMS links to health surveys.

### **6.2 Data Management**

All data will be collected in RedCap. When available, data collected by staff at each site will be submitted electronically to a protected online database. Pseudonymised data may be entered by study staff in order to minimize the workload on site clinical staff. Quality checks will be built into the data management system and there will be quality control checks of critical data points entered into the CRFs to ensure standardization and validity of the data collected. Patients' identities will be protected, and their information held securely. The records kept will not include any information that allows patients to be identified.

For both the Mpox Clinical Study and the internal pilot study, access to the data entry system will be protected by username and password. Username and password will be assigned during

the registration process for individual Site Investigators. All electronic data transfer between study site and database will be username and password protected. Each centre will maintain a study file including a protocol, ethics approval documentation, and paper CRFs. A participant list will be used in each study site to match identifier codes in the database to individual patients in order to record clinical outcomes and supply any missing data points.

The Participant List (enrolment log) is maintained locally and is not to be transferred to any other location, except the study coordinating centre to allow linkage with laboratory research findings. The sites will compile an enrolment log including the patient's name, date of birth, hospital identification number and unique study number. Subsequent data will be identified by the unique patient study number only (consist of a 3-digit site code and a 4-digit patient number; see section on Case Report Form and Patient Numbers). The enrolment log and study data will be kept separately.

## **6.3 Data Retention**

The value of detailed clinical information about acute disease and outcome caused by exposure to novel pathogens and other agents of public health interest is immense, particularly as the long-term sequelae cannot be predicted with certainty. Thus, we do not intend to destroy the data. Samples will be stored in the NCDC biorepository and data will be archived by NCDC. Access to data beyond this study will be in line with NCDC data protection and access policies.

## **6.4 Data Linkage**

For the purposes of deeper clinical characterisation and timely, well-targeted clinical trials in the patient population it is essential to link the current mpox Clinical Characterisation Protocol research records with routinely collected NCDC and related health and care records.

Participant identifiers will be used to request public health case surveillance data from NCDC.

Access to longitudinal patient records is vital for providing the fullest insights needed to respond to exposure to novel pathogens and other agents of public health interest in a timely and accurate manner. Researchers outside this study will only have access to the data relevant to their separate, ethically approved research questions and it will be provided in a de-identified form, which will be held in an accredited safe haven (trustworthy analytic environment), minimising the risk of inappropriate access to identifiable information. Use of the data will be fully audited and controlled.

Importantly, participant data collected in this study may be shared with other studies within the overall mpox project to facilitate recruitment to other studies; for example, data on a recruited confirmed case would be shared in real time, as long as the individual has provided consent, with the household transmission study in the mpox project, to facilitate identification of the household and approaching other members of that household for participation in the household transmission study.

## **6.5 Mpox Data Access and Data Sharing**

All use of depersonalised data, data including limited identifiers (e.g. national healthcare identifier) and biological samples will be controlled by the Data and Materials Access Committee.

### **6.5.1 Data and materials access committee**

The committee will comprise the Nigerian and UK co-leads for the overall mpox project and appropriate scientific advisers. NCDC will be represented on the committee.

All samples, generated data and materials will be governed by the committee. The committee will authorise use of samples and dissemination of results. Disputes will be resolved by majority vote of the committee. New appointments to the committee to replace retiring members will be proposed by the chair and approved by majority vote of the committee.

### **6.5.2 Principles of data and materials access**

The committee will facilitate and prioritise urgent investigations (from any sector, including public health, academic and commercial) with a high probability of impact in a given outbreak. Where appropriate, priority will be given to scientific work that can be completed within Nigeria, but data and samples may be analysed in other countries in collaboration with Nigerian researchers.

This study will recognise clinical investigators contributing to research efforts, often in extremely difficult circumstances. They will be given full recognition for their efforts and results from the study will be shared with them.

Data and results from central laboratory analysis for individual patients will be available to the clinicians looking after those patients as soon as possible. Often, this may not be in time to affect treatment decisions. Research data will be shared with public health authorities as needed.

## **6.6 Data Quality**

Several procedures to ensure data quality and protocol standardisation will help to minimise bias. These include:

- A start-up tutorial for all investigators, which may be online, will be held prior to study commencement to ensure consistency in procedures;
- A detailed data dictionary defines the data to be collected on the case report form;
- Quality checks will be built into the data management system and there will be quality checks of critical data points entered into the CRFs to ensure standardization and validity of the data collected;

Data queries may be generated, depending on resource availability. Any information that is not available for the investigator will not be considered as missing. No assumptions will be made for missing data.

### **6.6.1 Monitoring**

Data monitoring will be conducted on a randomly selected subset (up to 5%) of cases, through discussion of data collection techniques with the local site investigator. Direct site monitoring visits are preferred but may not be feasible for all sites; where this is the case, virtual site visits will be attempted.

## **7 Ethical Considerations**

This study is to be conducted during mpox outbreaks or presentations of cases of mpox in Nigeria. This is a challenging research situation because this falls in the area between clinical

care, public health and clinical research (WHO Ethical Review in Disease Outbreak Expert Meeting 2009).

Normally research activities are defined by anything conducted outside standard clinical care. In these situations, there may be no definitive standard guidelines or treatment protocols and therefore there is often little difference between what can benefit the patients and what is very important for building knowledge on the pathogenesis of the disease or exposure to guide future treatment and management.

Medical management of participants in this study and public health protection activities must never be compromised by study procedures. At all times, priority will be given to samples required for medical management and public health management. Research sampling should never compromise the quantity or quality of samples taken for medical management, nor create a significant diversion for clinical teams from the day-to-day care of the patients.

## **7.1 Regulations, Guidelines and Ethical Review**

This study will be conducted in compliance with the principles set out in the Declaration of Helsinki (Somerset West, 1996). Where applicable, the principles of Good Clinical Practice (ICH 1996) and other applicable regulations and guidelines will be used to guide procedures and considerations. The consent process for this study is described in section 3.4.

This protocol will be reviewed and approved by the ethical and regulatory review boards required by the recruiting site and the study sponsor. No patients will be enrolled until all approvals have been obtained for the applicable site.

## **7.2 Withdrawal**

Prospective participants are freely able to decline participation in this study or to withdraw from participation at any point without suffering any implied or explicit disadvantage. A withdrawal form should be completed by the research team for any participants who choose to withdraw from this study after providing consent. All patients will be treated according to standard practice regardless of if they participate.

## **7.3 Risks to Participants**

**Inconvenience.** Participation in this research study poses a minimal risk of inconvenience through attendance at research visits. Appropriate compensation for travel costs to attend any follow-up visits and for time of attending visits will be given according to the standard policies of the sponsor.

**Phlebotomy.** Participants may have blood drawn more often than is required for standard care. Phlebotomy can be associated with pain at the draw site and rarely with infection. Daily blood draw volumes have been restricted according to weight so that combined clinical and research sampling is within recommended limits. Discomfort will be minimized by having expert staff obtain blood samples, and by combining research sampling with routine clinical sampling, where possible, which normally occurs daily in acutely unwell patients in hospital.

**Discomfort of throat swabs.** Collecting throat swabs may cause transient discomfort. Discomfort and risk will be minimized by using experienced clinical staff at each site, and samples will be taken at the same time as clinical samples in order to minimize these risks.

**Incidental findings in genetic testing.** This study will NOT perform studies of human genomes; therefore, there are no associated risks concerning human genetic analyses (such as identifying a genetic marker of a disease) if a patient chooses to participate in this study.

**Potential to reveal a personal characteristic leading to stigmatisation and/or persecution.** Mpox is transmitted through close contact, which can include sexual contact. Revealing intimate and sexual encounters, and/or sexuality, may cause anxiety to a participant through fear of being identified, stigmatised or persecuted if that information became known to others. This clinical study asks very limited questions about transmission exposures (community exposure; exposed healthcareworker; vertical transmission; exposure to infected animal; unknown exposure). While these are not viewed as particularly sensitive categories, all data collected within the study are treated as strictly confidential. Furthermore, interviews of participants to collect such data will take place discreetly, so that others cannot hear or see the answers provided. More detailed exposure histories, including sexual contact histories, may be obtained if the patient also chooses to also participate in the separate transmission study; measures taken to inform participants, and safeguards to protect participants in that study, and their data, are described in the separate protocol and participant information sheets for the transmission study.

## **7.4 Benefits to Participants**

There will be no direct benefit to research participants. Participants attending research visits at a study-associated hospital or study-associated primary healthcare centre will have routine bloods tests performed at no cost to the participant and the results will be shared with the participants' clinicians (where applicable). Some participants would not ordinarily be able to pay for these tests themselves and, therefore, would the tests would not be performed if they were not participating in the study. Similarly, participants attending a research visit at a hospital will have a chest radiograph as part of the study if it's clinically indicated, something they may not have been able to pay for themselves.

The study may include biological sampling in addition to sampling required for medical management. The results of the tests done on these samples may not contribute to improving the participant's health. With the exception of routine clinical tests such as full blood count, biochemistry tests, blood cultures and chest radiographs, results of tests performed in this study will not be available in time to contribute to the participant's care. Where possible, test results with potential relevance to patient care will be informed to the participant and/or treating doctor. The feasibility of this will depend on local resources. Additionally, some assays cannot immediately benefit the patient because data will need to be pooled with others, or because the assays take time.

## **7.5 Participation in Other Research Studies / Co-enrolment**

In the case of emerging infections, including mpox, it is likely that other research projects, including clinical trials, will also recruit participants in this study. In fact, it is important that they do so, and great effort has been expended to ensure that this observational study is compatible with, and complementary to, other possible research projects.

## **7.6 Confidentiality**

This study will be conducted by clinical staff and those involved in the study will ensure that each study participant's privacy and confidentiality is maintained. Participants will not be identified in any published reports of this study. All records will be kept confidential to the extent provided by international and local law. All laboratory specimens, evaluation forms,

reports, study protocol, documentation, data and all other information generated will be held in strict confidence. No information concerning the study, or the data, will be released to any unauthorized third party.

Minimal personal data will be entered into the database for analysis. The participant's identifying personal information will be logged separately and stored securely. The participant might be asked to take part in future research, and therefore their identifiers need to be retained for contact at a future date, subsequent to the appropriate ethical approvals. The stored research data is also likely to be of significant value in the future for other studies and therefore permission is sought for this storing of the research data that does contain minimal patient identifiers such as age, sex and ethnicity.

The date of birth and postcode of participants will be collected to allow linkage with other health and social care datasets and to reduce data collection burden in support of other research activity including clinical trials. Where available, the participant's Epidemiological Number (assigned by states during their surveillance investigations) will also be recorded. Consenting participants will be provided with a paper copy of their consent form (if consenting via telephone this will be provided at the earliest opportunity). Electronic consent forms will be printed to allow for participants to be given a copy. Electronic consent is only permissible with explicit permission from the trial team, and will rely on printing of consent forms being possible and storage facilities meeting study requirements.

Paper and electronic medical records may be accessed during the study to confirm, verify or complete clinical information provided in the case report form.

Site files will always be accessible only to clinical and research staff. Consent will be sought for investigators to access patient data. Local research staff will access personal information, but all data will be pseudonymised before transfer by eCRF.

At the study research laboratories, all research samples will be labelled with a unique, non-identifiable subject number. The patient's name and subject number will be recorded on the consent form. This will preserve the link between pseudonymous and identifiable data. Data from routine clinical care will be pseudonymised and stored separately to laboratory samples. Samples obtained will be pseudonymised. The only link to identifiable clinical data will be the consent form. Further research questions, subject to appropriate ethical approval, may be answered in retrospect in the future. Since the samples and data generated by this work may be irreplaceable after an outbreak of mpox has passed, it is essential that future work is not impeded by unnecessary data loss.

Pseudonymised research data will be stored on managed computer systems at NCDC and other investigator sites relevant to the laboratory tests they have done. Only the study administrators will hold the data set key, and this will be separated from the personal identifiers. Data will be encrypted before transfer on portable devices. Multiple backups will be maintained on institutional servers. Critical data will be stored in encrypted form in a stable storage format with the passwords recorded on paper in securely held site files in these locations.

It is important that data generated now are not destroyed unnecessarily, since they will be of considerable potential value to future generations faced with similar outbreaks of infectious disease. Electronic data and electronic copies of paper documents will be stored indefinitely.



## 7.7 Custody of Data and Samples

Custody of site-specific study forms and the data they contain will remain with the responsible physician at the respective site.

Samples will be shipped to a central NCDC-associated laboratory for processing and pseudonymisation and later forwarded to research institutions for analysis as approved by the appropriate ethics/institutional review committee. Any residual samples will remain in the custody of the site until use can be decided upon according to Study policies/procedures. Transferred residual samples will be stored within NCDC's biorepository, which is the default storage site for all residual samples. Centralized data will be in the custody of NCDC. NCDC's data sharing policy will apply to this study.

## 7.8 Additional Ethical Considerations

**No right to withdraw data.** We do not intend to offer a mechanism to withdraw personal data that has already been collected. Withdrawal from the study will prevent any further data being collected and no further study visits or engagement with the participant will take place.

**Recruitment of critically ill patients who are not able to consent.** This is a ubiquitous problem in acute and critical care research and there is a clear legal framework under which these patients may be recruited to research studies. In all cases, efforts will be made to obtain informed consent from patients early in the course of illness, before critical illness interferes with their capacity to make decisions and to confirm consent at the earliest point in recovery. This principle applies equally to adults and children.

**Perceived coercion because of individual responsibilities to society, and the implications of this research for public health.** We are sensitive to the fact that some patients or their representatives may feel under an unusually strong moral obligation to participate given the nature of this research and the wide, and often inaccurate, publicity surrounding emerging infections. In view of this, we have tried to make both the potential benefits and limitations of this simple observational study clear in the information sheet. In the informed consent form, we also stress that participation is entirely voluntary and there is no penalty of any kind for declining to join the study.

**Balance between public health and research.** Patients with emerging infections are commonly the subject of public health investigations. The work proposed here is research and will be clearly presented as such. There is no primary gain to the patient from participating. In designing and describing this research we are clear that, in accordance with the guiding principles of Good Clinical Practice, the needs and autonomy of the individual are paramount and the potential benefits to wider society do not take precedence.

**Risks to clinical and research staff treating the participants.** Staff who enrol, examine and take samples from study patients are at risk of infection. Care of study participants will require increased sampling and contact frequency added to normally heavy clinical workloads. All staff must be trained in recognised infection control measures and have ready access to appropriate personal protective equipment. In collaboration with the public health authorities, there will be on-going communication with hospital staff to ensure the appropriate training is given, to support the work and to ensure that there is no excess burden on the health system. Where appropriate, dedicated research staff will be available to support the study activities.

**Use of digital photography and video.** Outbreaks of mpox have highlighted the need to characterise skin lesions and ensure consistency in swabbing from a given site or lesion. The wide availability of mobile video calls can now facilitate consent processes. We have included explicit consent to retain digital imagery of lesions. We will make best efforts to ensure that images are not disclosive of identity i.e. avoid face and distinguishing features such as tattoos and body piercings.

## **7.9 Insurance**

Arrangements are in place to provide for non-negligent harm arising from participation in the study, for which LSHTM is the Research Sponsor; however, if the study involves minimal deviation from normal clinical care, non-negligent harm cover may not apply.

## **7.10 Scientific and Peer Review**

A presentation of the study and a draft version (v00.06) of this protocol was reviewed by the Technical Steering Committee (TSC) of the UK Public Health Rapid Support Team, on 18<sup>th</sup> July 2022. Comments and suggestions received have been considered and, where appropriate, changes were made to the final protocol (version 1.0). The Investigators have provided a written response to all peer review comments from the TSC.

## **7.11 Publications, Presentations, and Knowledge Mobilisation**

It is anticipated that analyses of data from this study will result in one or more scientific articles in open-access, peer-reviewed journals. All findings will be shared with and approved by the study investigators, NCDC and UKPHRST prior to submission for publication. All scientific contributors to the study will be recognised through co-authorship or acknowledgement in publications, as appropriate. Collaborative authorship will be coordinated by the study leads and the chief investigators and will adhere to the rules on authorship published by the International Committee of Medical Journal Editors. Findings from the study may be presented at national and international conferences and seminars. Recognising that mpox is of international concern, findings may be presented to relevant international agencies, such as WHO, prior to publication. Important findings from the study will be explained to the wider public, in Nigeria and the UK, using established and effective communication and knowledge mobilisation tools.

## **7.12 Revision History**

## **8 APPENDICES**

To be used in combination with this protocol

## 8.1 Appendix A: Participant pathways



