

Global Mpox

Clinical Characterisation Protocol (CCP)

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## Background

## Rationale for the Study

Mpox has been a persistent public health issue in Central and Western Africa. The emergence of new virus variants and modes of transmission, and the expanding geographical spread in to previously non-endemic countries require investigation to improve knowledge about the disease in its various clinical manifestations and in different populations.

Characterising the clinical epidemiology of mpox disease caused by different virus clades and variants is important for the following reasons:

* Sensitive and specific clinical and public health case definitions are required for case detection and management: this requires high-quality clinical epidemiology data. The current absence of widespread sensitive, specific, rapid, and affordable diagnostics tests increases the importance of clinical case definitions.
* Identification of groups at high risk of complicated disease, who can be targeted for preventative measures or enhanced clinical management, requires high quality clinical epidemiology data.
* Good understanding of the natural history, prognosis and outcomes of disease is needed to design intervention studies and to evaluate interventions.
* Establishing, and then monitoring, the clinical epidemiology is necessary to identify changes over time that may require modification of clinical or public health responses.

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## Objectives of the Collaboration

The main objective of the collaboration is to comprehensively characterise and compare the clinical epidemiology of mpox disease caused by different virus clades/subtypes in various populations and over time.

This will be achieved by creating a prospective observational study that will collect and analyse information to characterise the clinical presentation, natural history, risk factors and outcomes of all circulating mpox clades and variants.

The collaboration will utilise a series of available clinical characterisation tools developed by ISARIC and already approved and in use in several jurisdictions, including for mpox in Africa.

The collaboration will facilitate collection and harmonising data from different settings and populations, and following trends over time, while also enabling centres to conduct high-quality, expert-informed local research. The knowledge generated will help inform better case management, clinical trial design, and public health interventions.

## Background Information

Human mpox (previously known as monkeypox) was first described in 1970 in the Democratic Republic of Congo (DRC). There are 2 major genetic clades of monkeypox virus (MPXV), Clade I and Clade II.

Historically, clade I MPXV circulated in 5 countries – the Democratic Republic of the Congo (DRC), Nigeria, Gabon, the Republic of the Congo, and Central African Republic (CAR). However, recent years have seen an escalation in the frequency and severity of outbreaks, as well as geographical expansion into previously unaffected areas including Burundi, Kenya, Rwanda, and Uganda. In 2023 a new variant (clade Ib) was identified from an outbreak in the DRC that has spread to several countries. Whether this variant is more transmissible or causes more severe disease is not known. This ongoing outbreak has caused over 18,000 cases with an approximate case fatality rate of 5% - most of these in children. The African CDC declared this outbreak a Public Health Emergency of Continental Security (PHECS) on 13 August 2024 and the WHO declared a Public Health Emergency of International Concern (PHEIC) on 14 August 2024.

It also became apparent in 2022 that clade II MPXV has evolved into two main sub-clades: IIa and IIb. Clade IIb MPXV (mostly subclade IIb B.1) 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. Over 90,000 cases have been reported so far during the global glade IIb outbreak with an estimated case fatality rate of 0.2%.

## 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 in response mode, to address important gaps in public health and clinical knowledge and support clinical trials in response to outbreaks.

Significant experience has been gained in using the CCP (e.g., just under a million CRFs completed for COVID-19 globally), leading to important advances in understanding emerging infections. The ISARIC-WHO CCP (and associated case reporting form (CRF)) has been used to study patients with mpox in the UK in 2022, in Nigeria since 2024, and in Rwanda and the DRC since 2024 to study patients with mpox. Furthermore, database structures, statistical analysis plans, and python code 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.

## Enrolling in resource limited settings

The study will be conducted at multiple sites across multiple countries. It is appreciated that settings may vary in terms of clinical infrastructure, resources, and capacity. Even for a given site, capacity may reduce if there is a surge in patient presentations. 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. 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.
* **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)**: As for tier one, but with repeated biological sampling during the course of illness and recovery.

## Study Objectives

### Primary Objectives

Our primary objectives for mpox are to:

* Describe the demographic, clinical, and laboratory features of patients with mpox, irrespective of clade, variant, or lineage
* Describe the clinical course and outcomes of patients up to 28 days following enrolment, and compare these between clades, variants and lineages.
* Determine demographic, clinical, and laboratory predictors of disease severity, disease outcome, and transmission and compare these characteristics between clades, variants, and lineages.
* Describe, where appropriate, the use of vaccines and treatments, including supportive care, and novel mpox treatments if they are used as part of clinical care during the study period.

And, where feasible depending on laboratory capacity:

* Describe characteristics of mpox viruses causing human mpox infections, including features that may be associated with disease severity, and/or transmission (such as genotypic or phenotypic changes in viruses detected that are known to alter transmission) and to compare these characteristics between clades, variants, and lineages.
* 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
* 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

### Secondary Objectives

Our secondary objectives are to collect evidence to:

* Improve identification, triage and clinical management of people with mpox
* Improve infection control measures for mpox
* Inform the development of evidence-based clinical and policy guidance documents.

## Study Design

This is a prospective observational cohort study with clinical data collection and, in some sites, biological sampling.

## Inclusion criteria

Potential participants are eligible for inclusion if they

1. Have a new laboratory confirmed diagnosis of MPXV infection

AND, OR

1. Present with an acute illness that is clinically suspected*a* to be mpox*b*.

*aThe study is not applying case definitions for enrolment because this will restrict enrolment and bias the clinical characterisation towards pre-existing definitions.*

***b****until the point at which an alternative cause of illness is confirmed and/or mpox is subsequently and confidently excluded. Data from those participants 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*.

## Exclusion criteria

* The participant has previously been enrolled in this cohort.

## Study procedures

## Practical considerations

Detailed information on how to implement study procedures will be provided in standard operating procedures and the study laboratory manual. Study operations will be streamlined and embedded in clinical workflow to minimise additional effort.

**Location of visits**

Participants will be asked to attend a research visit at a site associated with the study or will receive a visit from study staff (for hospitalised patients, and some outpatients depending on the location). If a participant declines attendance at a study site, or this is infeasible, telephone or internet follow up can occur.

**Flexibility**

Where assessments are undertaken for clinical need (e.g. RT-PCR), these are not duplicated as a study-specific procedure. Sampling for clinical need is always prioritised before research sampling for this study.

There is deliberate flexibility in the data and biological sampling schedules to reflect operational challenges and potential variability in available sampling resources at different sites/locations. Where possible, all visits should be completed for a given tier. Where it is not possible to complete all visits, this will not result in a protocol violation, but the reason for a visit being omitted should be recorded. A preferred order is contained below to prioritise the most important samples where there are foreseen resource limitations.

## Identification of Potential Participants

Potential participants will be identified from the point that a clinician in a participating clinical site is

1. notified of a positive *MPXV* result by the laboratory.
2. Reviews a patient for an acute illness and believes they have mpox.

Patients are eligible for enrolment at any point during their acute illness.

When resources limit the number of patients enrolled to less than the number of patients presenting, sites will establish procedures to minimize bias in the selection of participants. Laboratory confirmed cases will be prioritised for data collection.

## Consent

Written informed consent will be required prior to a participant being enrolled in the study.

A participant information sheet (PIS) will be provided and explained. Where necessary, it will be translated 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.

All potential participants will have the opportunity to ask questions about the study prior to providing consent. Participants who agree to participate will be asked to sign and date an informed consent form with the following modifications

* Children: Consent will be given by parents/guardians for children who are too young to provide consent themselves, according to national standards for age of consent. Children will be asked for their assent to participate.
* Adult patients unable to consent from themselves: Consent to participate will be given by next of kin or an acceptable (defined by national research regulations) proxy or representative or consultee.
* Adult patients who are illiterate: The consent process will be witnessed by a healthcare professional who will sign the consent form.
* Participants who cannot understand the language of the available forms: Verified translations will be made when possible. If it is not possible, verbal translation of the document will be used. In this case, the translator may act as the witness for consent and sign the consent form.
* If a patient is incapable of giving consent and there is no relative/representative present: All efforts will be made to have consent from appropriate consultee /guardian/carer when available, and from the patient at the earliest opportunity. In the interim, depending on national regulations, 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.

In some situations, the proxy consent giver may be confined under conditions of quarantine or self-isolation. In these circumstances consent will sought by telephone or voice-over-internet communication using a telephone-witnessed form.

If provided, consent may be withdrawn at any time. Declining participation in the study, or withdrawal from the study will not influence or impact the patient’s clinical care or management of their case by Public Health authorities.

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

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.

## Schedule of assessments

**Table 1: Clinical data collection timeline**

|  |  |
| --- | --- |
| **Clinical journey** | **Element of case reporting form** |
| **DAY OF RECRUITMENT**  **Date of recruitment** | Consent form  Complete ADMISSION and DAILY FORM |
| **EACH DAY OF ACUTE ILLNESS**  **until *outcome* achieved** | Complete another DAILY FORM |
| **If applicable: DAY OF ICU DISCHARGE** | Complete a DAILY FORM |
| **DAY OF OUTCOME**  **Inpatients = Day of hospital discharge**  **Outpatients = Day of discharge from care** | Complete OUTCOME FORM |
| **DAY >28 FOLLOW UP**  **Convalescent follow up** | Update OUTCOME FORM |

**Table 2: Biological sample collection timeline**

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Study Day | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 | 28+\* |
| Collect sample set | Y |  | Y |  | Y |  |  |  | Y |  |  |  |  | Y | Y |
| Priority of Sample^ | 1 |  | 2 |  | 5 |  |  |  | 3 |  |  |  |  | 6 | 4 |

\*Convalescent sample collected any single day between day 28 – 56

^If local resource limitations require sampling frequency to decrease, samples will be prioritised as shown (1=highest priority).

#### TIER ZERO schedule – Clinical data only

Clinical data (according to the schedule in table 1) are collected and entered into the CRF, including the results of any laboratory testing performed for clinical reasons. 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.

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

In addition to collecting clinical data (according to the schedule in table 1), a single research sample set is obtained at recruitment (Day 1), or as soon as practical following recruitment. The contents of the sample set are defined in table 3.

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

In addition to collecting clinical data (according to the schedule in table 1), a serial research sample sets are according to the schedule in table 2. The contents of the sample set are defined in table 3.

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).

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.

**Table 3. Tier 1 and Tier 2 research sample set – to be obtained at each sampling point.**

|  |  |  |
| --- | --- | --- |
| 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 | Full blood count, renal profile, liver profile, bone profile, blood glucose, HIV serology, CD4 count (if HIV test is positive) |
| Pathogen samples:   * Throat swab sample in viral transport medium * Urine (up to 10ml), do not fill the container * Stool (up to 10ml) if produced; * Mpox swab samples (minimum of two, maximum of four) in virus transport medium from mpox lesions and infected sites/vesicles/ulcers/sores/mucosa * Shed mpox lesion scabs if produced * Also store any residual volumes from samples taken for clinical care e.g. CSF | 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 double bagged.  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 (e.g. weekends/public holidays) store in refrigerator until processing. For details, see Laboratory Manual.

## Medical Management of Participants

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, and in some case biological specimens; therefore, adverse event reporting is not applicable, as there is no intervention. Results of any clinically-relevant tests performed, including haematology and biochemistry blood tests, 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.

## Follow-Up Procedures for Participants

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).

## 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.

## Specimens and Laboratory Analysis

Specimen sampling, storage procedures and transport requirements are detailed in the study laboratory manual.

Paediatric samples will be reduced in volume according to standard procedures. Standard care samples will be prioritised over research samples if volume reduction is required. Ability to take samples is dependent on staff availability, the availability of suitable laboratory facilities and caseload. Research samples may therefore be reduced or missed if needed to maintain care standards and staff safety, and to reflect the assays that can be performed by the laboratory attached to a treatment facility.

Samples will not be duplicated if they are collected on the same day for clinical reasons.

## Statistical considerations

A detailed, pre-specified statistical analysis plan will be prepared in advance of the primary analysis.

**Sample size considerations**

This is a descriptive study of a re-emerging infectious disease, with cases and outbreaks occurring somewhat unpredictably. The larger the number of included patients, the more robust and precise the findings of the study. 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.

## Data

### Data Collection

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 (pseudoanonymised). The enrolment log and study data will be kept separately.

All study data will be collected in RedCap.

All data access will be controlled by unique usernames and passwords, and any changes to data will require the user to enter their username and password as an electronic signature in accordance with regulatory requirements. Staff will have access restricted to the functionality and data that are appropriate for their role in the study.

### Data Movement

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.

The Participant List (enrolment log) is maintained locally and is not to be transferred to any other location, except the study coordinating centre if required to allow linkage with laboratory research findings.

### Data Retention

The value of detailed clinical information on rare emerging infections is immense. Thus, we do not intend to destroy the data. Samples will be stored in within country biorepository where possible and data will be archived by the national principal investigator.

### Data Access and Data Sharing

Patients will be asked if they consent to secondary use of their data and/or biological samples.

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

The committee will be chaired by the Chief Investigator and comprise the national principal investigators (or a named delegate for each and appropriate scientific advisers. New appointments to the committee to replace retiring members will be proposed by the chair and approved by majority vote of the committee.

Any proposed plans to use samples other than for those investigations detailed in this protocol must have approval by to the relevant ethics committees prior to any approvals from this committee.

The committee will authorise use of samples and dissemination of results. Disputes will be resolved by majority vote of the committee. 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 Africa, but data and samples may be analysed in other countries in collaboration with nationally based researchers.

### Data Quality and Monitoring

Several procedures to ensure data quality and protocol standardisation will help to minimise bias. These will be detailed in study specific standard operating procedures and may 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 standardisation and validity of the data collected;

Data monitoring will be conducted according to a study specific data monitoring plan. 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.

## 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.

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.

## 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 will be restricted according to weight (detailed in standard operating procedures) so that combined clinical and research sampling is within recommended limits. Discomfort will be minimized by combining research sampling with routine clinical sampling, where possible.

**Discomfort of** **throat** **swabs.** Collecting throat swabs may cause transient discomfort. Samples will be taken at the same time as clinical samples in order to minimize these risks.

**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 questions about transmission exposures (community exposure; exposed healthcare worker; vertical transmission; exposure to infected animal; unknown exposure). Whether additional, more sensitive questions, (such as history of sex with a same-sex partner) are asked, will depend on guidance at a national level and will be restricted to countries where a)the national principal investigator and community representatives feel there is negligible risk of stigma or harm to the participant by asking the question b) the behaviour is not illegal in the country. 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 here or see the answers provided.

## Benefits to Participants

There will be no direct benefit to research participants. Participants attending research visits at a study-associated site will have routine bloods tests performed at no cost to the participant and the results will be shared with the participants’ clinicians (where applicable).

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, and blood cultures, 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.

## Reimbursement of participants

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 performed as part of the study protocol. Reasonable travel expenses to attend study visits will also be paid.

## 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.

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

## Administration, Sponsorship and Insurance

## Publications and Knowledge Mobilisation

The findings from this research will be published open-access, peer-reviewed journals following approval of the study investigators. All contributors will be recognised through co-authorship or acknowledgement following International Committee of Medical Journal Editors guidelines. Results may be presented at national and international conferences. Findings of public health relevance may be presented to relevant international agencies, such as WHO, prior to publication. Key findings will be communicated to the public.

## 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.

## Revision History

## APPENDICES