

# Ethics: Example Response Text

This document is designed to provide you with assistance when completing your ethics application. An ethics application may not be required in every context. This provides examples of commonly asked questions on application forms and template answers relating to the Global CCP which can be adapted to your local requirements and practices.

Example responses can be found for each of the following questions below:

Brief Scientific Background
Is this a clinical trial?
Primary objective
Secondary objective
Design and methodology
How many patients will be recruited/ Sample size?
List the clinical procedures being undertaken as part of the research
Give the total volume of blood to be taken for research
Will participants' genetic material be analysed?
Is permission for genetic testing requested in the consent form?
Will subjects be recruited from the following groups?
How will patients be identified and approached?
Are there any potential benefits to participants?
Are there any ethical issues from the participants' or researchers' perspective?
What are the potential risks?
How will personally identifiable data be handled?
Who will be able to access patients' personally identifiable data and health records?
Has the study received peer review?

# Ethics: Example response text

Guidance is provided in [blue text](#) and should not be copied to your application.

## Brief Scientific Background

### ALL APPLICATIONS

Infectious disease is the single biggest cause of death worldwide. New infectious agents, such as the SARS, MERS and other novel coronavirus, novel influenza viruses, viruses causing viral haemorrhagic fever (e.g. Ebola), and viruses that affect the central nervous system (CNS) such as TBEV & Nipah require investigation to understand pathogen biology and pathogenesis in the host. Even for known infections, resistance to antimicrobial therapies is widespread, and treatments to control potentially deleterious host responses are lacking.

In order to develop a mechanistic understanding of disease processes, 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 pathogen, the dynamics of the host response, the pharmacology of antimicrobial or host-directed therapies, the transmission dynamics, and factors underlying individual susceptibility.

### SPONSOR

The work proposed here is an observational study set which requires collection of patient data with or without sampling that will not immediately benefit the participants. It also requires analysis of the host genome, which may reveal other information about disease susceptibility or other aspects of health status. All information and analysis of patient samples will be anonymized at all times and will not be tracked back to the patient.

### SITE

*Include the following text if you are participating in sampling (Tier 1, 2 or 3)*

The work proposed here requires sampling that will not immediately benefit the participants. It also requires analysis of the host genome, which may reveal other information about disease susceptibility or other aspects of health status.

## Is this a clinical trial?

### ALL APPLICATIONS

No.

## Primary objective

### ALL APPLICATIONS

Our primary objectives are to:

- Describe the clinical features of the illness or syndrome and identify risk factors for more severe disease.
- Describe, where appropriate, the response to treatment, including supportive care and novel therapeutics.

### SPONSOR and SITE

*Include if you're taking part in research sampling (Tier 1, 2 or 3)*

- Observe, where appropriate and feasible, pathogen replication, excretion and evolution, within the host, and identify determinants of severity and transmission using high-throughput sequencing of pathogen genomes obtained from respiratory tract, blood, urine, stool, CSF and other samples.

- Characterise, where appropriate and feasible, the host responses to infection and therapy over time, including innate and acquired immune responses, circulating levels of immune signalling molecules and gene expression profiling in peripheral blood.
- Identify host genetic variants associated with disease progression or severity.
- Understand transmissibility and the probabilities of different clinical outcomes following exposure and infection.

### Secondary objective

ALL APPLICATIONS

Secondary objectives are to collect evidence in order to:

- Facilitate effective triage and clinical management of patients with infections relevant to this protocol.
- Develop clinical guidance documents and offer clinical recommendations to policy makers on the basis of evidence obtained.

SPONSOR and SITE

*Include if you're taking part in research sampling (Tier 1, 2 or 3)*

- Determine infectivity and inform appropriate infection control measures of the various pathogens.

### Design and methodology

ALL APPLICATIONS

This study is a prospective, observational cohort study.

The study will be conducted at multiple sites (to be determined by the spread of disease and availability of resources). It is appreciated that settings will 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.

In all cases, a proportionate case report form (paper CRF or web-based electronic "eCRF") will be completed. Most of the clinical data can be entered retrospectively from medical records

Tiers included in this protocol are:

- Tier 0 (Clinical data collection only) – Clinical data will be collected but no biological samples will be obtained for research purposes. The minimum clinical data set will summarize the illness episode, clinical characteristics on admission, severity and outcome, with the option to collect additional key clinical data at frequent intervals, according to local resources/needs.
- Tier 1 (Single biological sample) - Clinical samples will be collected on enrolment day (Day 1; ideally at initial presentation to a health care facility). Clinical information will be collected at enrolment (within 24 hours of admission) and discharge, with the option to collect additional key clinical data at frequent intervals, according to local resources/needs.
- Tier 2 (Serial biological sampling) - Clinical samples and data will be collected on enrolment day (Day 1; ideally at initial presentation to a health care facility), and then alternate days for the first 2 weeks, then weekly until resolution of illness or discharge from hospital, and again at 3 and 6 months after enrolment.
- Tier 3 (Population pharmacokinetics of antimicrobial/immunomodulatory drugs)

Each site will recruit at a given tier. This will be recorded in the site file "Tier Record Form". Changes to the tier at a given site will be documented by the PI.

This protocol will be opened at sites with capacity and capability to recruit to specific tiers. The study has no set end date.

Samples required for clinical management will at all times have priority over samples taken for research tests. Aliquots or samples for research purposes should never compromise the quality or quantity of samples required for medical management. Wherever practical, taking research samples should be timed to

coincide with clinical sampling. The research team will be responsible for sharing the sampling protocol with health care workers supporting patient management in order to minimize disruption to routine care and avoid unnecessary procedures.

Some samples should be processed and stored at -80°C (Table 1). We recognize that -80°C storage is not available at all sites. In this case please store at coldest available temperature and at least -20°C.

### How many patients will be recruited/ Sample size?

#### ALL APPLICATIONS

This is a descriptive study of a syndrome, which may be caused by a number of different known or poorly understood pathogens. Therefore, the sample size is not prospectively determined. Recruitment of participants will depend on the emergence and spread of the various pathogens and the resources available to the recruitment centres. The sample size will vary for each location, but should be as large as feasible and preferably without limit in order to capture as much clinical data as possible early in the outbreak.

### List the clinical procedures being undertaken as part of the research

#### SPONSOR AND TIER 1, 2 & 3 SITE APPLICATIONS

#### ADDITIONAL TEXT FOR SPONSOR:

Those sites participating in Tier 0 will not be undertaking sample collection or other clinical procedures for research purposes.

#### Tier 1:

A single sample set is obtained at, or as soon as practical after, recruitment ('**recruitment sample set**'). Record data in CRF.

Consider giving a brief description of:

1. The Procedure e.g. Nose swab;
2. Whether this sample is routinely taken, and the number of sample routine samples being taken
3. Whether this sample is specific to research, and the number of research samples being taken
4. Timing e.g. daily weekly and over number of months,
5. The time taken per procedure,
6. Who will carry-out the procedure?

#### Tier 2:

A '**recruitment sample set**' is obtained followed by schedule-dependent '**serial sample sets**' e.g. Days 3 and 9: Serial biological samples, including pathogen samples AND blood sample at 3 and 6 months post recruitment. Record data in CRF.

Consider giving a brief description of:

1. The Procedure e.g. Nose swab;
2. Whether this sample is routinely taken, and the number of sample routine samples being taken
3. Whether this sample is specific to research, and the number of research samples being taken
4. Timing e.g. daily weekly and over number of months,
5. The time taken per procedure,
6. Who will carry-out the procedure?

#### Tier 3:

A '**recruitment sample set**' is obtained followed by '**serial sample sets**' e.g.

- Days 3 and 9: Serial biological samples, including pathogen samples AND blood sample at 3 and 6 months post recruitment.
- Day 5; plus weekly (until 100 days); Plus Day 7; Plus Day 11: Serial biological samples, including additional pathogen samples on days 7 & 11).

Record data in CRF.

Consider giving a brief description of:

1. The Procedure e.g. Nose swab;
2. Whether this sample is routinely taken, and the number of sample routine samples being taken
3. Whether this sample is specific to research, and the number of research samples being taken
4. Timing e.g. daily weekly and over number of months,
5. The time taken per procedure,
6. Who will carry-out the procedure?

### Give the total volume of blood to be taken for research

Maximum volumes that may be taken.

TIER 0 SITE APPLICATIONS:

n/a

TIER 1 SITE APPLICATIONS ONLY:

>40kg: maximum 15ml

20 to 40kg: maximum 12ml

10 to 20kg: maximum 6ml

4 to 10kg: maximum 2ml

<4kg: maximum 0.8ml.

TIER 2 & 3 SITE APPLICATIONS:

>40kg: maximum any day 15ml; maximum during any 4 weeks 96ml

20 to 40kg: maximum any day 12ml; maximum during any 4 weeks 42ml

10 to 20kg: maximum any day 6ml; maximum during any 4 weeks 23.6ml

4 to 10kg: maximum any day 2ml; maximum during any 4 weeks 9.4ml

<4kg: maximum any day 0.8ml; maximum during any 4 weeks 2.4ml.

### Will participants' genetic material be analysed?

SPONSOR AND TIER 1, 2 & 3 SITE APPLICATIONS:

Yes.

TIER 0 SITE APPLICATIONS :

n/a.

**Is permission for genetic testing requested in the consent form?**

SPONSOR AND TIER 1, 2 & 3 SITE APPLICATIONS:

Yes

TIER 0 SITE APPLICATIONS :

n/a

**Will subjects be recruited from the following groups?**

ALL APPLICATIONS:

Pregnant women: Yes

Children under 18: Yes

People with learning difficulties: Yes

Unconscious or severely ill: Yes

**How will patients be identified and approached?**

SUGGESTED TEXT FOR ALL APPLICATIONS – text should be adapted according to local practice:

In hospital, potential participants will be identified through primary care, health clinic or hospital workers upon presentation at recruiting sites. Participants may also be identified through public health agencies. Consent will be taken by professionals trained in taking informed consent. 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.

Patients will only be considered for enrolment if appropriate local infection control and prevention measures are in place and can be maintained.

Where patients lack capacity to consent to participation, an appropriate representative/ consultee/ parent/ guardian 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 participant or parent/ guardian/ consultee and allow them time to discuss and ask questions. The staff will review the informed consent form with the person giving consent and endeavour to ensure understanding of the contents, including study procedures, risks, benefits, the right to withdraw at any time for no reason and alternatives to participation. The consenting party will be asked to sign and date an informed consent form. If the patient is a child, the person with parental responsibility and the child, if competent, should both provide consent/ assent.

An outbreak involving a pathogen of public health interest or pandemic is an emergency. Patients who are incapable of giving consent in emergency situations are an exception to the general rule of informed consent in clinical research. This is clearly acknowledged in the Declaration of Helsinki (2008). The process of consent will comply with the principles of Good Clinical Practice and with the laws regulating clinical research in the recruiting centre.

ADDITIONAL TEXT FOR SPONSOR AND TIER 1, 2 & 3 SITE APPLICATIONS:

In view of the importance of early samples, participants or their parent/ guardian/ consultee will be permitted to consent 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.

TIER 0 SITE APPLICATIONS CONSIDER THE BELOW TEXT ACCORDING TO LOCAL REQUIREMENTS

For studies that collect or collate only anonymised data that is normally collected, as part of routine care consent may not be required.

Waiver of consent / low / negligible or minimal risk:

Due to the importance of complete case ascertainment, that only de-identified data are submitted, and the potential benefits of the research to the wider community, we are seeking to streamline data collection and ask that consent be waived.

Waiver of consent is requested because this study is a population-based, epidemiology study.

This research involves no intervention and all clinical information will have been collected as part of routine clinical care by health care workers who normally have access to health care records.

We believe this research carries only a low risk to participants.

The major potential risk is breach of privacy and this is minimised by mandatory submission of de-identified data. It is unlikely to be feasible for sites to participate if consent is required.

This study involves the collection of protected health information (PHI) only by the participating site who have legitimate access to this data. The collection and retention of PHI by sites is necessary to ensure data integrity. Examples of identifiers collected include: enrolment date; onset/admission dates; collection dates of any pathogen testing; outcome data; sex and delivery date of live/still birth in the case of pregnant woman being enrolled.

PHI data will be de-identified before entering data into the central study database. The information collected does not include information that may be damaging to the individual should it be wrongfully disclosed.

### Are there any potential benefits to participants?

#### ALL APPLICATIONS

There will be no direct benefit to research participants during this outbreak, but participants may benefit by the outputs from this research in the event of future outbreaks.

#### SPONSOR AND TIER 1, 2 & 3 SITE APPLICATIONS:

The study will 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 during this illness episode. The results of 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. Some assays cannot immediately benefit the patient because data will need to be pooled with others, or because the assays take time.

### Are there any ethical issues from the participants' or researchers' perspective?

#### ALL APPLICATIONS

**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 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 direct 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 enroll, 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 recognized 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.

**What are the potential risks?**

TIER 0 SITE APPLICATIONS

Overall responsibility for ensuring that each participant’s information is kept confidential will lie with the Study Sponsor.

Any paper documents will be stored securely and kept in strict confidence in compliance with the Data Protection Act (1998).

IF USING ALERRT DATA PLATFORM

Web-based data management software is available to support data entry of the ALERRT CRF, via the ISARIC data platform. This includes online data capture and a mobile app. Sites can choose to set up independent studies or contribute to combined data analysis. Data are entered on the central electronic REDCap database at <https://ncov.medsci.ox.ac.uk> or to your site/network’s independent database. Printed paper CRFs may be used for later transfer of the data onto the electronic database. REDCap is a secure web platform for building and managing online databases, hosted by the University of Oxford. All information entered onto the database will be anonymized and the University of Oxford will not be able to identify patients from these records. Data ownership will remain with the Data Submitter. Full details of how the data will be handled is detailed in the Terms of Submission [ENSURE A COPY OF THE TERMS OF DATA SUBMISSION IS INCLUDED IN ANY APPLICATION E.G. ETHICS/IRB APPLICATION].

SPONSOR AND TIER 1, 2 & 3 SITE APPLICATIONS

**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 respiratory swabs**

Collecting respiratory 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.

**Discomfort of lumbar puncture**

Collection of cerebrospinal fluid with lumbar puncture will only be performed if clinically indicated, as decided by the responsible physician. Clinical investigations are the priority, with any remaining sample collected for use in research. Guidance on the safe recommended daily total volume of CSF to take in different age groups is provided (table below). Lumbar puncture can be associated with discomfort at the site of needle insertion, headache, and rarely bleeding or infection.

Estimates of CSF production rate, total CSF volume and the safe recommended CSF volume taken at lumbar puncture for different age groups. Taken from the British Infection Society guidelines for the diagnosis and treatment of tuberculosis of the central nervous system in adults and children (2009).

Age	Mean CSF production rate (ml/h)	Total CSF Volume (mls)	Safe CSF volume to take at LP (mls)
Adult	22	150-170	Maximum: 15-17



Adolescent	18	120-170	Maximum: 12-17
Young child	12	100-150	Maximum: 10-15
Infant	10	60-90	Maximum: 6-9
Term Neonate	1	20-40	Maximum: 2-4

**Incidental findings in genetic testing**

This study includes genetic testing to identify host genetic variants associated with disease progression or severity. There is a very small chance that these tests may result in the incidental discovery of information that is relevant to the participant's health. Since the samples will be analysed anonymously in batches, and generally in non-clinical laboratories with investigational techniques, we will not attempt to identify and inform participants of any results from genetic tests. If we were to do so, there would be a considerable risk of accidental harm in the form of unnecessary anxiety and distress.

TIER 2 AND 3

**Inconvenience**

Participation in this research study poses a minimal risk of inconvenience through household visits and attendance of follow-up visits.

**How will personally identifiable data be handled?**

ALL APPLICATIONS

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 [\[SPONSOR, TIER 1, 2 & 3 SITE APPLICATIONS ONLY\]](#), 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.

Site files will at all times 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 clinical data will be anonymized before transfer to electronic Case Record Form (eCRF).

Consent forms will need to be stored in a secure way locally, separately from the CRFs.

[WHERE USING THE ISARIC CASE REPORT FORM AND DATA PLATFORM] Participant Identification Numbers consist of a site code and a 4-digit participant number. Registration and provision of a site code can be obtained by contacting [ncov@isaric.org](mailto:ncov@isaric.org). Participant numbers should be assigned sequentially for each site beginning with 0001.

[IF USING THE ISARIC DATA PLATFORM] Data are entered on the central electronic REDCap database at <https://ncov.medsci.ox.ac.uk> or to your site/network's independent database. Printed paper CRFs may be used for later transfer of the data onto the electronic database. REDCap is a secure web platform for building and managing online databases, hosted by the University of Oxford. All information entered onto the database will be anonymized and the University of Oxford will not be able to identify patients from these records. Data ownership will remain with the Data Submitter. Full details of how the data will be handled is detailed in the Terms of Submission [\[ENSURE A COPY OF THE TERMS OF DATA SUBMISSION IS INCLUDED IN THE APPLICATION\]](#).

It is important that data generated now is 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 for at least 5 years.

**Who will be able to access patients' personally identifiable data and health records?**

*SUGGESTED TEXT FOR ALL APPLICATIONS – text should be adapted according to local practice*

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. When the study team reviews patient notes, they are bound by professional confidentiality.

*[WHERE USING THE ISARIC DATA PLATFORM]* All clinical data will be stored anonymously in secure databases only accessible to study staff. Study sponsors and health authorities will be given controlled access for the purpose of audit when necessary.

**Has the study received peer review?**

*ALL APPLICATIONS*

The proposed research is the product of several years of discussion within a group of international experts who were brought together following the 2009 influenza pandemic to plan the global research response to future severe and emerging infections: the International Severe Acute Respiratory and Emerging Infection Consortium (ISARIC). ISARIC working group 3 (genomics, pathogenesis and pharmacology) comprised senior clinical scientists from five continents working together to promote and harmonise observational research during outbreaks of severe infectious disease.