Disclaimer

This document is a draft and the information contained herein is subject to change as this document is currently undergoing review by the World Health Organization Ethical Review Committee.

The final version of this standardized protocol: *Natural History Protocol for Zika Virus Infection* will be published as soon as the ethical review has been completed.

Standardized Protocol:

Natural History Protocol for Zika Virus Infection

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More information on IDAMS can be found on their website: http://www.idams.eu
More information on ISARIC can be found on their website: https://isaric.tghn.org

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PROTOCOL SUMMARY

The purpose of the **Natural History Protocol for Zika Virus infection** is to simply, rapidly and systematically collect standardized clinical information, in order to describe important features of Zika virus infection. These include but are not limited to symptomatology, clinical course, and risk factors for severe disease and complications. This investigation will often occur in areas with co-circulating arboviruses such as chikungunya and dengue viruses, and may help elucidate if prior or co-infection with these viruses may alter a patient's clinical presentation or prognosis.

This standardized protocol employs a flexible structure so that it can be adapted for use in various clinical settings such as: the outpatient, district or tertiary hospital settings in order to gather clinical information on participants in a rapid and coordinated manner. This involves the collection of clinical information using a tiered approach including the use of standardized case report form(s) (CRFs), including a rapid Zika virus CRF which serves as a minimal data set as well as the ability to collect more detailed information using population specific CRFs (eg. neonate, pregnant women CRFs etc). In addition, there is also a tiered approach to biological (laboratory) sampling protocol that study sites can implement based on local resource availability.

This protocol will help to fill major knowledge gaps in the current understanding of the natural history and clinical characterization of ZIKV infection across all age groups. It has been designed to maximize the likelihood that data and biological samples are systematically collected and shared rapidly in a format that can be easily aggregated, tabulated and analyzed across many different settings globally. The intent is that this protocol can be utilized easily by primary care practitioners and also those working in district and tertiary hospitals.

We encourage all centres to contribute to this effort regardless of resource availability or patient volume. Ownership of the primary data remains with the individual sites.

Other protocols currently under development include:

- Case-control study to assess potential risk factors related to microcephaly including Zika virus infection
- Case-control study to assess potential risk factors related to Guillain-Barré Syndrome including Zika virus infection
- Prospective longitudinal cohort study of women and newborns exposed to Zika virus during the course of pregnancy
- Prospective longitudinal cohort study of newborns and infants born to mothers exposed to Zika virus during pregnancy
- Prospective longitudinal cohort study of Zika-infected patients to measure the persistence of Zika virus in body fluids

- Cross-sectional seroprevalence study of Zika virus infection in the general population

Study groups may decide to implement several protocols during a ZIKV epidemic. In this case, participants may be enrolled in several studies (e.g. cohort of pregnant women and ZIKV persistence study). However, each study group needs to consider carefully the burden on each participant.

Comments for the user's consideration are provided in purple text throughout the document, as the user may need to modify methods slightly as a result of the local context in which this study will be carried out.

Information that should be completed by the local study site is provided in red text throughout the document.

CONTENTS

LIST OF ABBREVIATIONS

Ab	Antibody
Ag	Antigen
CHIKV	Chikungunya virus
CMV	Cytomegalovirus
CONSISE	Consortium for the Standardization of Influenza Seroepidemiology
DE	Design effect
HIV	Human Immunodeficiency virus
HSV	Herpes Simplex virus
ICC	Intracluster correlation
IgG	Immunoglobulin G
IgM	Immunoglobulin M
IHR	International Health Regulations
IRB	Institutional Review Board
ISARIC	International Severe Acute Respiratory and Emerging Infection Consortium
LCMV	Lymphocytic choriomeningitis virus
ME	Margin of error
PAHO	Pan American Health Organization
PBMC	Peripheral Blood Mononuclear Cell
PRNT	Plaque-reduction neutralization test
RNA	Ribonucleic acid
RPR	Rapid plasma reagin
RT-PCR	Reverse transcriptase-polymerase chain reaction
SST	Serum separator tube
TORCHS	Toxoplasmosis, other (e.g. varicella), Rubella, Cytomegalovirus, Herpes, HIV, Syphilis
TPHA	Treponema pallidum hemagglutination assay
VZV	Varicella zoster virus
WHO	World Health Organization
WMA	World Medical Association
YFV	Yellow Fever virus
ZIKV	Zika virus

1.0 INTRODUCTION

An ongoing outbreak of Zika virus (ZIKV) is affecting many countries worldwide. The WHO declared a Public Health Emergency of International Concern (PHEIC) on 1 February 2016 over major concerns regarding an association between ZIKV disease and microcephaly/other neurologic disorders (1). On the 18 November 2016, the WHO Emergency Committee (EC) declared the end of the PHEIC and that a robust longer-term technical mechanism was now required to manage the global response and that ZIKV remains a significant enduring public health challenge, which requires intense action (http://www.who.int/mediacentre/news/statements/2016/zika-fifth-ec/en/). This protocol aims to contribute to the long term and robust global research response.

ZIKV, Chikungunya virus (CHIKV), and Dengue viruses (DENV) are all transmitted by the same *Aedes* mosquito vector, often co-circulate and may be endemic in many affected countries. CHIKV was first described in 2013/14 and ZIKV in 2015 in the Latin American region (2, 3). The clinical presentation of these three arboviral infections, as well as other causes of non-specific febrile illnesses may be difficult to differentiate and individuals may present with co-infections with more than one of these arboviruses. Information regarding ZIKV is increasing but many important knowledge gaps on the natural history of ZIKV still exists.

This natural history protocol employs a tiered approach to clinical data collection and is designed for use in a variety of settings: outpatient, district and tertiary hospitals. The protocols tiered approach that allows local study sites to modify the implementation of the protocol (e.g. timing and frequency of biological sampling) based on local resource availability and local ethics approval.

In the attempt to understand the natural history of ZIKV infection this protocol aims to describe the full spectrum of clinical manifestations including frequency and severity in patients presenting with ZIKV of all ages, as well as potentially identify risk factors associated with severe clinical manifestations or complications of ZIKV. Importantly, this will occur in the context of co-circulating CHIKV and DENV, to determine if prior or co-infection with these viruses may alter the clinical presentation or prognosis. The background immune landscape may prove important in populations in the current ZIKV outbreak areas who may have been exposed to DENV and CHIKV in the past and are now being exposed to ZIKV for the first time.

[*** Insert - information about the epidemiology of the outbreak in the country conducting this study is provided in Appendix A. This includes up to date research results available before submission to a local/national Ethics research Committee (ERC) or Institutional Research Board)***].

CLINICAL FEATURES AND PATHOGENESIS OF ZIKV, CHIKV, and DENV INFECTION

Given the overlapping clinical syndromes of ZIKV, CHIKV and DENV a brief description of current understand of clinical features and brief pathogenesis is included below.

ZIKA VIRUS INFECTION (ZIKV)

Although most ZIKV infections are asymptomatic, amongst those who experienced symptoms with confirmed ZIKV infection on Yap Island during the 2007 outbreak the most common symptoms were maculopapular rash (90%), fever (65%), arthritis or arthralgia (65%), non-purulent conjunctivitis (55%), myalgia (48%), headache (45%), retro-orbital pain (39%), edema (19%), and vomiting (10%) (4). During the current South American outbreak, rash, itching, prostration, headache and arthralgia (with or without edema) have been reported most frequently in the first four days of disease (5). Fever at presentation was not observed in the majority of these patients (64%) (5). Given the variations in clinical presentations in different outbreaks, it remains important to continue to gather information about clinical features and the different presentations of ZIKV infection in order to determine true frequency of these different clinical features. In addition, differences in clinical manifestations and sequelae of ZIKV infection in different age groups and different geographical locations requires further study.

Congenital anomalies are associated with ZIKV infection during pregnancy, though the absolute and relative risks are not yet definitively known. This will be evaluated by cohort studies currently underway (see WHO Standardized Protocol: Prospective longitudinal cohort study of newborns and infants born to mothers exposed to Zika virus during pregnancy protocol). Additional risk factors for microcephaly also need to be evaluated as potential effect modifiers given varying frequencies of microcephaly being reported amongst different countries within Latin America (see WHO Standardized Protocols: Case-control study to assess potential risk factors related to microcephaly including Zika virus infection in pregnancy and Prospective longitudinal cohort study of woman and newborns exposed to Zika virus during the course of pregnancy).

Risk factors for severe neurological manifestations (e.g. Guillain-Barré Syndrome) are also currently being evaluated (see WHO Standardized Protocol: Case-control study to assess potential risk factors related to Guillain-Barre Syndrome including Zika virus infection). Severe neurological disease following ZIKV might still be a rare event, however, the frequency and clinical spectrum of all neurological manifestations including transient and less severe disease is not known.

The exact incubation period of ZIKV infection is unknown, however, it is likely similar to that of other mosquito-borne flaviviruses (i.e. generally less than 1 week) (4). The viremic period is estimated to last less than one week after onset of symptoms, however, recent studies have suggested prolonged viremia can occur in certain populations, such as pregnant women (6). (See WHO Prospective longitudinal cohort study of Zika-infected patients to measure the persistence of Zika virus in bodily fluids for more information).

Although WHO has developed an interim case definition for ZIKV infection in an effort to provide global standardization of classification and reporting of Zika cases, in view of the variability in clinical

presentation, laboratory confirmation is considered desirable (7). Please refer to the most up to date WHO case definition as this may change as more data become available.

Table 1, WHO interim case definition for ZIKV disease (WHO 12 February 2016) (7):

Suspected case:
A person presenting with rash and/or fever and at least one of the following signs or symptoms:

- arthralgia; or
- arthritis; or
- conjunctivitis (non-purulent/hyperemic).

Probable case:
A suspected case with presence of IgM antibody against ZIKV [1], and an epidemiological link [2]

Confirmed case:

- A person with laboratory confirmation of recent ZIKV infection:
- presence of ZIKV RNA or antigen in serum or other samples (e.g. saliva, tissues, urine, whole blood); or
- IgM antibody against ZIKV positive and PRNT90 for ZIKV with titre ≥20 and ZIKV PRNT90 titre ratio ≥ 4 compared to other flaviviruses; and exclusion of other flaviviruses

Notes:
[1] With no evidence of infection with other flaviviruses
[2] Contact with a confirmed case, or a history of residing in or travelling to an area with local transmission of ZIKV within two weeks prior to onset of symptoms.

DENGUE VIRUS INFECTION (DENV)

Most DENV infections are asymptomatic. Symptomatic cases present with a range of clinical manifestations from mild febrile illness to severe and fatal disease. Symptoms may include headache, myalgia, arthralgia, retro-orbital pain, bone pain, anorexia, vomiting, rash and hemorrhagic manifestations (8). The current classification system adopted in the latest WHO dengue guidelines (2009) classifies the disease into dengue and severe dengue, with the hope that this will prove more effective for triage and clinical management, and will also improve the quality of surveillance and epidemiological data collected globally (9, 10).

Relatively little is known about DENV disease pathogenesis, particularly in relation to the mechanisms responsible for the systemic vascular leak syndrome (11). Although all four viral serotypes can cause fatal disease, second or subsequent infections are much more likely to be associated with severe clinical manifestations than primary infections (12, 13). Evidence indicates that severe disease is associated with higher plasma viral loads, and implicates immune response mechanisms to the virus in playing a significant role in pathogenesis (14, 15).

CHIKUNGUNYA VIRUS INFECTION (CHIKV)

In contrast to ZIKV and DENV, the frequency of asymptomatic CHIKV infections appears to be relatively low. Patients typically experience a sudden onset of high-grade fever. The constellation of symptoms that follow may include arthralgia, myalgia, headache, photophobia and rash (16). Arthritis can be a disabling symptom and usually manifests as a relapsing, symmetrical polyarthralgia preferentially affecting distal joints (17, 18). The characteristic skin manifestations in adults are a maculopapular rash with or without pruritus. In children, bullous rashes with sloughing, or petechial rashes may occur (19). Hemorrhage appears to be rare, and minor when it does occur (17). For most patients, symptoms resolve within 7-10 days (18). Fatal illness is rare but can occur (18, 20). Encephalitis has also been described (21). Persistent arthralgia is a frequent complication of CHIKV infection and may persist from months to years (17, 22). The average incubation period for CHIKV is between 2-4 days (19).

There is limited understanding of CHIKV pathogenesis compared to other alphaviruses. Following inoculation from a mosquito, CHIKV initially infects and replicates in skin cells (including dermal fibroblasts and macrophages), before dissemination to lymph nodes and blood (23). Subsequently, CHIKV appears to preferentially replicate in skeletal muscle, connective tissue and tendons, consistent with the predominance of musculoskeletal clinical manifestations (24). There is an association between viral load and clinical severity.

1.1 OBJECTIVES

The aim of this protocol is to describe the natural history of ZIKV infection including clinical presentations in different age groups and geographic locations, and possibly identify risk factors for severe disease manifestations and complications in the context of co-circulating arboviruses.

The **primary objectives** of this study are to:

- To capture the full spectrum and frequency of clinical manifestations associated with ZIKV across all age groups.
- To identify clinical and/or simple laboratory parameters, which differentiate ZIKV from other febrile illnesses that fit the inclusion criteria – especially other arboviruses like CHIKV and DENV

The **secondary objectives** of this study are to:

- To assist in a refined clinical case definition for ZIKV.
- To describe the role of co-existing or past infection with DENV or CHIKV and the association with the clinical phenotype of ZIKV infection.
- To identify clinical and/or simple laboratory parameters among patients infected with ZIKV that are associated with complications, should more complicated manifestations be identified as part of the spectrum (see primary objectives) or severe ZIKV infection.

[*** insert - additional secondary objectives may be included in the protocol by the country conducting this study, this should be informed by the outbreak characteristics and by the local context***].

Technical, financial or capacity limitations may limit the amount of participants a particular site can enroll. However, this study protocol is designed so that smaller studies, each of which have followed the methodology described below, may be aggregated in order to achieve larger participant numbers to identify the spectrum of clinical findings.

It is important to note that this protocol is designed to describe the core data set and methodology requirements in order to address the primary objectives. As such, the implementation of this study may include additional objectives or study components, as determined by the financial and technical capacity of the country/study group implementing this protocol and by the outbreak context.

2.0 STUDY PROCEDURES

This is a prospective, multi-center, observational study of ZIKV, an emerging pathogen. This protocol will be open for recruitment for [*** insert – years as appropriate ***].The protocol is designed to gather clinical information on participants in a rapid and coordinated manner.

Patients of all ages presenting with a febrile/rash illness or symptoms consistent with possible diagnosis of ZIKV,(see Table 2) to various clinical settings, including outpatient, district or tertiary healthcare facilities [***insert country/region(s)***] will be eligible for enrolment (see inclusion criteria for further information). The main clinical study will be coordinated by [*** insert name of institution(s) ***]. The study will be conducted in accordance with International Council for Harmonization – Good Clinical Practice (ICH-GCP) guidelines, with regular oversight by a team of independent monitors.

The two main components of the protocol include the collection of clinical information, which includes history and physical examination , as well as laboratory sampling which will be collected on case report forms (CRFs). The frequency of data gathering will depend on the study setting. It is expected that frequency of data collection, laboratory sampling and follow-up will increase, as resources are available in district and tertiary settings.

Clinical history and examination findings will be recorded in standard CRFs. CRF selection will be based on resources and time available to complete the CRFs. For those situations where only rapid and basic information can be collected (eg.in a setting with low resources or where there are no ongoing cohort or case-control studies), the CRFs titled “Zika Virus Rapid Case Report Form” (See Appendix B) and/or “Zika Virus Rapid Follow-up Case Report Form” (see Appendix C) should be utilized. In settings with more resources or ongoing studies it is preferred to use a more detailed population specific CRF(s) whenever possible (see https://zikainfection.tghn.org/research-tools-and-resources/crfs/ for complete list of CRFs based on population or Appendix D). In the absence of studies in the area, the “Zika Virus Rapid Case Report Form” can rapidly help to gather clinical information and help to fill in gaps.

The laboratory sample(s) which should be obtained according to a tiered algorithm based on local resource availability, together with standard hematological and biochemical parameters to be determined by the participants treating physician. The tiered approach is to facilitate each site choosing the amount of data to be collected based on available site resources (See Figure 1 and Table 1). Each study site may choose to enroll study participants in different tiers as their resources allow. Study sites may also choose to change enrollment tiers over the course of the study based on patient volumes, for example first 50 patients could be enrolled in Tier 2 and the remainder in Tier 1 or 0.

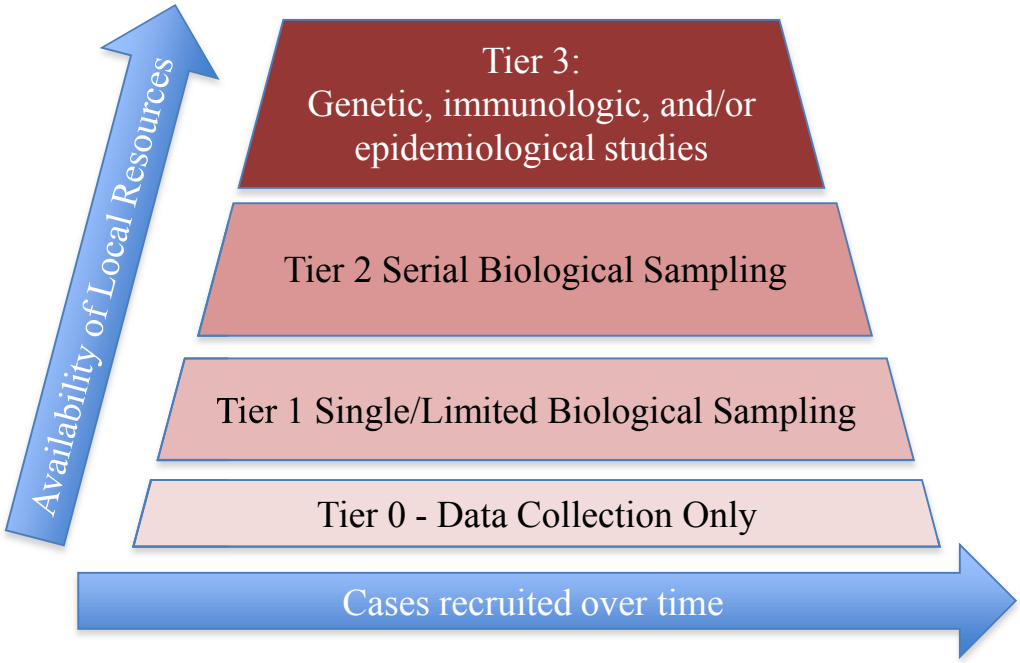

Figure 1. Tiered approach of study participant recruitment.

Figure 1 above provides a brief overview of the tiered approach that can be utilized for the recruitment of study participants. This protocol provides an approach to observational studies on the natural history of ZIKV, and allows for flexibly based on available resources. Each tier builds upon the previous tier, eg example the data collected for patients recruited to Tier 2 would include all of the data from Tier 0 and 1 as well. In addition to this each tier is independent from the next and analysis will occur per tier. Eg the individuals who are in Tier 2 and not the same as those who were recruited into Tier 1 for example.

Figure 2 below provides an overview of the complete Zika Virus Infection Natural History Protocol.

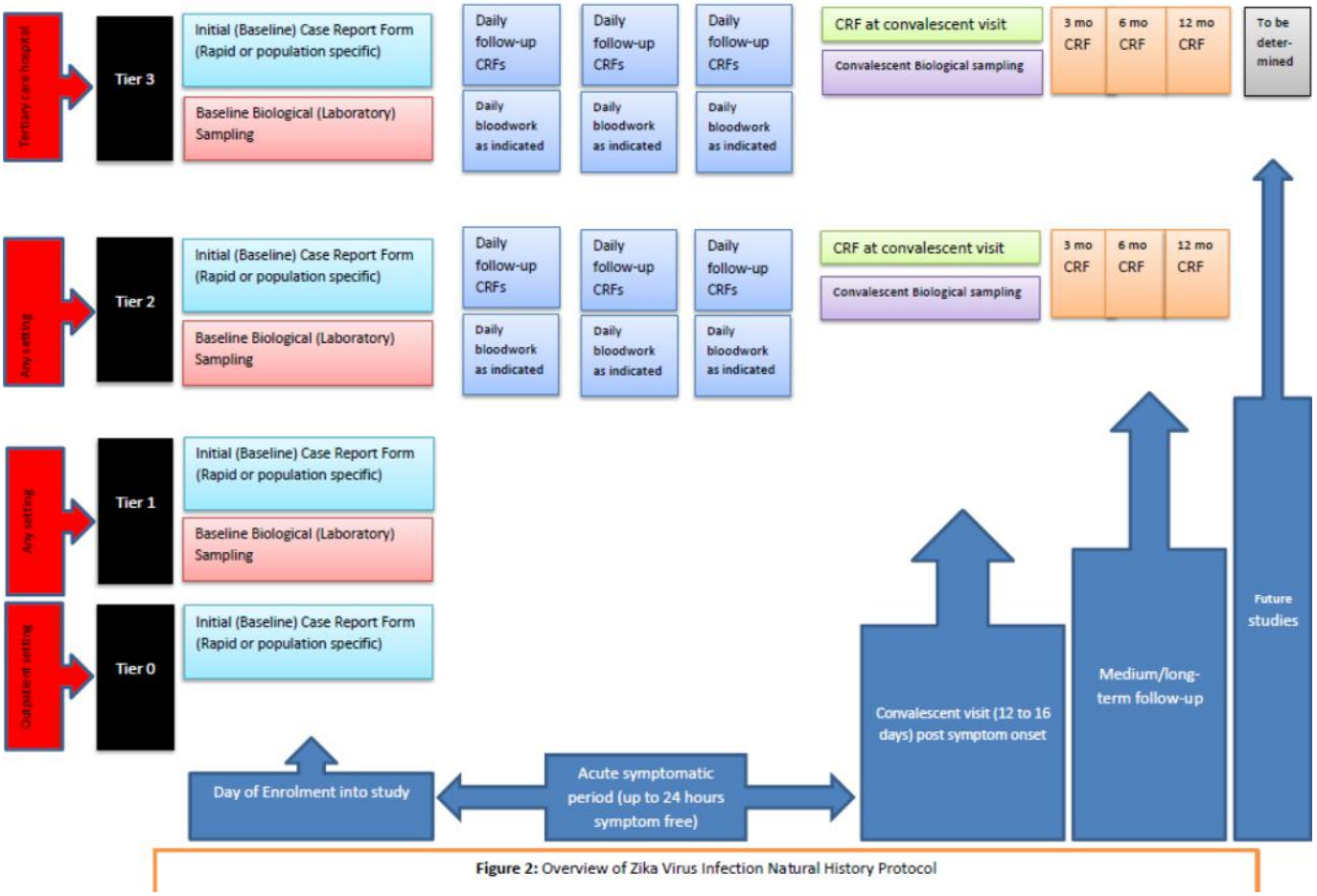

Figure 2: Overview of Zika Virus Infection Natural History Protocol

Table 1 below provides guidance on when and which CRFs should be used to gather clinical information regarding study participants, in the context of the tiered approach.

Table1 Details on case report form (CRF) selection and stratified based on tiered approach

TIER	When/how to use it	CRF selection	Setting
[**TIER 0**] Data collection at enrolment only NO BIOLOGICAL SAMPLES ARE TAKEN IN THIS	**NOTE:** The use of this tier alone is less useful than Tier 1 as no laboratory diagnostic confirmation would occur and should only be used when no laboratory facilities exist. Complete the initial/baseline CRF only at the time of enrolment in the study.	Complete: Zika Virus Rapid CRF OR Complete any Baseline and	Outpatient setting.

TIER.	For low resource sites without laboratory facilities.	Outcome CRFs for specific populations (based on resources)	
[**TIER 1**] Data collection at enrolment and single/limited biological sample	Complete Tier 0 + single biological sampling at the time of enrolment in the study (see Table 3). For low resource sites, or; For rapid data collection during an outbreak/epidemic; or during an epidemic for sites that have already enrolled large numbers of patients on the Tier 2 schedule.	Complete: Zika Virus Rapid CRF OR Complete any Baseline and Outcome CRFs for specific populations	Any setting including: Outpatient setting, District and Tertiary hospitals
[**TIER 2**] Data collection at enrolment and serial biological sampling, including baseline (IDEAL TIER)	In addition to completing Tier 0 and 1 there are three major components to Tier 2 **Component 1:** DAILY follow-up CRFs during the symptomatic period and up to 24 hours after symptoms abate. Serial laboratory sampling as per clinical need. **AND** **Component 2.** Includes component 1 + biological (laboratory) at the convalescent visit at 12-16 days after illness. **AND** **Component 3**. Includes component 1 and 2 + Long-term follow-up of participants at 3 months, 6 months and 12 months* involving CRF completion.	Complete: Zika Virus Rapid CRF OR Any Baseline and Outcome CRFs for specific populations + Any Laboratory Results CRF for specific population (for hospitalized patients If patient admitted to ICU: Any Intensive Care CRF for specific population If completing Component 3:	Any setting including: outpatient, District and Tertiary hospitals with available resources.

		Follow up visit CRF for specific population including neurodevelopmental outcomes as appropriate	
	For Tier 2 IDEALLY COMPLETE COMPONENTS 1, 2 AND 3 described above. If a site can only complete partial components If only partial for example Components 1 and 2 only, this still fits into this ties and still useful.		
[**TIER 3**] Genetic and immunologic studies;	Complete Tier 0, 1 and 2 and assess collect laboratory samples relevant to Tier 3 (which may be stored for future use).	N/A	If resources are available at any site (most likely at tertiary hospital)
and/or epidemiological studies	Complete Epidemiological studies in combination with any other study at Tier 0, 1, 2 and 3	Demographic and Epidemiology CRF	If resources are available at any site (most likely at tertiary hospital)

*This is a suggested follow up schedule, however ideally in Tier 2, individuals should be followed up to a minimum of a year. Follow-up may be extended beyond this time period as clinically indicated and as resources allow. This is particularly relevant for neurodevelopmental follow-up which would likely involve longer follow-up for 2 years or longer. The suggested follow-up after one year would be 18 months and 24 months.

2.1 SELECTION AND RECRUITMENT OF STUDY PARTICIPANTS

2.1.1 STUDY POPULATION

Participants of all ages are eligible for enrolment provided they meet the inclusion criteria outlined below. This study can be implemented in areas with an emerging outbreak or in areas where ZIKV is well established.

This is a prospective, multi-center, descriptive observational study of an emerging pathogen about which little information is known, therefore, sample size calculation is not applicable. The recruitment of participants may vary for each location but should be as large as possible (preferably without limit) in order to capture as much clinical data as possible early in the outbreak. Any site, regardless of size, that is interested in collecting data regarding ZIKV infection is encouraged to participate. The tiered approach has been designed in such a way that even sites with limited

participant volumes or limited resources can still collect and contribute data. If there is a specific case control or cohort study occurring in the same area, study sites may choose to preferentially enroll participants who qualify into those studies in lieu or in addition to this study.

2.1.1 IDENTIFICATION OF STUDY PARTICIPANTS

Participants of all ages may be recruited from any setting including: the outpatient, district and tertiary settings.

2.1.2 ELIGIBILITY CRITERIA

Inclusion criteria:

Participants of all ages presenting for care to any setting with the following symptoms and provide informed consent:

- Rash at presentation OR history of rash within the preceding 96 hours
  OR
- Fever at presentation (>= 37.5 ^{o}C/ 99.5 ^{o}F axillary or >=38 ^{o}C/100.4^{o}F sublingual/rectal) OR history of fever within the preceding 96 hours
  OR
- Clinical symptoms consistent with possible acute ZIKV infection (see Table 2)
  OR
- Undifferentiated fever or rash in an individual from a ZIKV, CHIKV, or DENV endemic area (e.g. returning traveler).

Exclusion criteria:

- Localizing features suggestive of an alternative diagnosis which better explains the fever and/or rash, e.g. pneumonia, otitis media, eczema etc.
- Participant, parent, or appropriate representative does not consent to participate or does not have the mental capacity to provide informed consent to participate.
- Laboratory confirmed alternative diagnosis compatible with patient illness

Table 2: Clinical Symptoms consistent with ZIKV (1-3, 15-17)
Please note list is not exhaustive, nor does it equate to a case definition, and is not in order of frequency of symptoms.

Maculopapular rash	Headache
Pruritis	Retro-orbital Pain
Fever	Edema
Arthritis/Joint Pain	Vomiting
Conjunctivitis	Acute myelitis
Prostration (marked loss of strength)	Severe disease: meningoencephalitis, Guillain-Barre Syndrome, Congenital Zika Syndrome

2.2 ETHICAL CONSIDERATIONS

This study will be conducted during a disease outbreak. This is a challenging research situation, which falls within the domains of clinical care, public health, and clinical research (WHO Ethical Review in Disease Outbreak Expert Meeting 2009). Normally research activities are defined as anything conducted outside standard clinical care. In outbreak situations, especially those involving novel pathogens, 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 required to build knowledge on the natural history of the disease to guide future treatment and management.

Clinical management of the study participants will be carried out according to standard of care at the treating site and is not a part of this research protocol. Medical management, routine diagnostic tests and laboratory testing performed for clinical care will be available as per the local standard of care and take priority over the study biological sampling and should never be compromised by study procedures. At all times, priority will be given to laboratory samples required for medical management. As this is an observational study, adverse event reporting is not applicable. If therapeutic interventions become available over the course of the study period (e.g. intravenous IgG or vaccines) their use should be documented in the CRF.

ZIKV/DENV/CHIKV diagnostic tests may be performed on blood and urine samples from participants suspected of having ZIKV.

Ethical approval will be sought in accordance with local, regional and national authorities prior to study initiation. The sponsor and the investigators will be committed to conducting this research in accordance with the World Medical Association (WMA) Declaration of Helsinki (Ethical Principles for Medical Research Involving Human Subjects) adopted by the 64th WMA General Assembly, Fortaleza, October 2013 (http://www.wma.net/en/30publications/10policies/b3/index.html).

2.2.1 BENEFITS/RISKS FOR STUDY PARTICIPANTS

Risks

The risks involved with participation in this study are minimal. The tier in which the participant is enrolled will determine if venepuncture is required or not. Venepuncture can be distressing for young children and some adults. Bruising and very rarely infection can occur at venepuncture sites. Collection of a blood sample for a full blood count is often part of the standard of care for participants with fever without focal signs and therefore most participants would undergo this procedure whether enrolled in the study or not. A follow-up blood sample (convalescent sample) may not usually be performed after two weeks, but is important for the conduct of the study. Follow up at 3, 6 and 12 months will not routinely involve further venepuncture unless clinically indicated.

Unexpected incidental findings may infrequently be identified in individual study participants in the course of any clinical study. If this occurs, the participant and/or consultee will be informed and, with

their consent, a referral will be made to an appropriate clinic or health facility for further investigation or follow up. We will maintain confidentiality about their participation in the study.

Benefits

The primary benefit of this study (depending on tier of the study participant) is the extended medical care and intensified (i.e., beyond routine) follow-up provided to participants, which will allow for timely detection of any abnormality or complications and for appropriate clinical management. Venepuncture risks described above are offset by the fact that study participants in tier 2 and above will be assessed daily during the acute phase of illness so that complications and/or alternative diagnoses will be identified early and addressed early.

Potential benefits from the results of clinical and biological sampling will be directly translated into implementation in the countries affected by ZIKV activity.

All research tests and study-related medical consultations will be paid for by [***Insert name of Sponsor identified in country***]. [Local site to insert reimbursable expenses***] will be reimbursed for attendance at follow-up visits according to the national wage and per diems designated by each site.

2.2.2 INFORMED CONSENT

During initial enrollment interview, the purpose of the study will be explained, and written informed consent obtained by a trained member of the investigation team. Potential participants/consultees will be given up to 96 hours after the onset of illness to decide if they wish to participate in this study. After 96 hours has passed the participant will no longer be eligible for the study.

Each study participant will be informed that their participation is voluntary and that they will be free, without justification, to withdraw from the study at any time without consequences. Written informed consent will be collected from all study participants or consultee as appropriate. Written informed assent will be collected for minors participating in the study who are capable of assenting. Informed consent/assent will seek approval to collect clinical information plus possible biological samples from study participants for study purposes, based on tier. The possibility that samples may be shipped outside of the home country for additional testing and/or analysis and those samples may be used for future research purposes is included in the consent/assent form. The consent/assent forms will also indicate that any suspected or confirmed ZIKV infection may be notified to national authorities under the International Health Regulations (IHR) requirements.

The member of the investigation team is responsible for obtaining the written consent/assent of the participant and answering any questions the participant may have. Contact information for the study team will be provided for any new questions, which may arise. If the study participant agrees, the consent form must be completed legibly, with both surname and first name, dated and signed by the participant and the member of the investigation team in duplicate, before any procedure can be performed as part of the current study.

The original version of the consent/assent form for each participant will be retained by the investigation team and kept in a secure place for a period of 15 years after end of research. A copy will be given to the study participant.
Informed consent/ assent form templates for participation in the study are in Appendix E.

Every effort will be made to provide consent/assent forms in the country's national language if it is not possible to prepare a translation in a required language, verbal translation of the document and the consent discussion will be provided. In this case, the translator may act as the witness for consent and sign the consent form so that participants who cannot read the language of the forms are not excluded from participating in this research. Illiterate participants may have the consent form read to them in the presence of a witness, who will sign to verify the accurate reading of the form and agreement of the participant.

In the case of adult participants who are unable to provide informed consent due to mental or physical status, the wishes of the participant may be declared by a designated 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 consent independently, informed consent should be re-discussed and obtained, and participant should be withdrawn upon their request.

Parents or guardians of children under the age of [***insert minimum age of consent in your country/region***] would provide consent for their child. Study staff obtaining consent will consider the ability of the child to understand the basic principles of the study and will discuss the study with the child using age appropriate language. Where appropriate, children age 12 years to [***insert minimum age of consent in your country/region***] will be invited to give assent, which will be recorded on the assent form. The right to withdraw at any time without negative impact will be reinforced with the child and their parent/guardian.

2.2.3 CONFIDENTIALITY

All information collected in this study will remain confidential. Data will be stored securely in a password-protected database and CRFs and laboratory samples will be labeled with a study identification number only and stored in suitable secure locations.. If a participant consents/assents to participate, they will be assigned a Study Identification Number provided by the local study site. This identification number will include the site number and patient number designated at site country level [***insert here the site and patient code - number of digits to be used for the study***]. Participant's names will be recorded at the time of enrolment to allow for their identification at follow-up visits. However, identifiable information will be linked to stored data or samples only by a protected Master List with the study identification number.

When available, the site/country decides to use a central database (depository of data worldwide). The identification number will include the site number [3 digits] and patient number [5 digits] XXX-XXXXX. For example, the identification number 003-00250, refers to site 003 and patient number 00250. The site number is allocated automatically when the site is registers to upload study data to the central database (see section 2.3).

No identifying information will be transferred between sites. Only study personnel who have signed the locally appropriate data protection commitment form will have access to the password-protected computer where data is stored. After conclusion of the project, data will be removed from the computers and stored in a secure location. No individual participant will be identified by name or initials in any publications or reports generated from the data. When the research team reviews their charts, they are also bound by professional confidentiality.

2.3 DATA COLLECTION AND MANAGEMENT

2.4.1 DATA COLLECTION

After informed consent/assent is obtained from eligible study participants, clinical and laboratory data will be collected according to local resource availability using the tiered approach described above. Priority at all times will be given to the collection of clinical information required for patient care. Data collected for research purposes will be extracted and integrated as much as possible with information available from chart files. Clinical data will be collected using appropriate CRFs, to be completed by the study staff (see collection of clinical information below).

Upon the discretion of the study site, it is suggested that a rapid access card be provided to the study participant [***insert brief description for facilitating access of patient to follow up***] to facilitate daily follow-up in the clinic, communicate important medical information (e.g. complications), and provide the contact information of the local study team. Standardized clinical information will be recorded and blood work may be ordered based on tier.

The clinical management including the need for routine blood work will be at the discretion of the treating physicians and this information can be collected and transcribed into the CRF(s). Any study participant recruited from an outpatient setting who goes on to require hospital admission should be continued to be followed daily using population specific CRFs (available in the Appendix D), with the indication(s) for admission clearly documented, and all management interventions recorded together with the physician's rationale for these interventions.

Collection of clinical information

Table 3 provides guidance on when and which CRFs should be completed to gather clinical information regarding study participants, in the context of the tiered approach and based on resources and time availability.

Table 3: Details on case report form (CRF) selection based on tiered approach

TIER	When/how to use it	CRF selection	Setting

[**TIER 0**] Data collection at enrolment only NO BIOLOGICAL SAMPLES ARE TAKEN IN THIS TIER.	Complete CRF(s) at the time of enrolment in the study only.	Complete either: "Zika Virus Initial Case Report Form: Rapid Form" (Appendix B) (Time/resource limited). Note: skip questions 129-180 OR All of the following CRFs (Appendix D): "Acute symptoms" & "Baseline and Outcome" for specific populations**, and "Epidemiology and Demographics" CRF:(If time/ resources available)	**NOTE:** The use of this tier alone is less useful than Tier 1 as no laboratory diagnostic confirmation would occur and should **only** be used in low resource outpatient settings where no laboratory facilities exist.
[**TIER 1**] Data collection at enrolment and single/limited biological sample	Complete Tier 0 + single biological sampling at the time of enrolment in the study (see Table 4).	Complete either: "Zika Virus Initial Case Report Form: Rapid Form" (Appendix B) (Time/resource limited). OR All of the following CRFs (Appendix D): "Acute symptoms" & "Baseline and Outcome" & "Laboratory results" for specific populations**, and "Epidemiology and Demographics" CRF:(If time/ resources available)	For low resource sites in any setting (outpatient, district or tertiary hospital), or; For rapid data collection during an outbreak/epidemic; or during an epidemic for sites that have already enrolled large numbers of patients in Tier 2.
[**TIER 2**] Data collection at enrolment and serial biological sampling, including baseline (IDEAL TIER)	In addition to completing Tier 0 and 1 there are three major parts to Tier 2 **Part 1:** DAILY follow-up CRFs during the symptomatic period and up to 24 hours after symptoms abate. Serial laboratory sampling as per clinical need.	For Part 1 and 2 Complete either: "Zika Virus Initial Case Report Form: Rapid Form" (Appendix B) AND Zika Virus Follow-up Case Report Form: Rapid Form" (Appendix C) (Time/resource limited).	Any setting including: Outpatient setting, District and Tertiary hospitals

	AND **Part 2**: CRF completion & Biological (laboratory) sampling at the convalescent visit (12-16 days after illness onset). **AND** **Part 3**:Long-term follow-up of participants at 3 months, 6 months and 12 months* involving CRF completion.	OR All of the following CRFs (Appendix D): "Acute symptoms"& "Baseline and Outcome" & "Laboratory results" for specific populations** and "Epidemiology and Demographics" and "Follow-up" (Appendix D) If patient admitted to hospital or ICU: Use appropriate "Hospital Stay" and/or "Intensive Care" CRF for specific population** (Appendix D) If completing Part 3 use "Follow-up" CRF for 0-5 year (Appendix D)	
	*For Tier 2 IDEALLY COMPLETE PARTS 1, 2 AND 3 described above. If a site can only complete some parts for example Parts 1 and 2 only, this still fits into this Tier 2.		
[**TIER 3**] Genetic and immunologic studies;	Complete Tier 0, 1 and 2 and collect laboratory samples relevant to Tier 3 (which may be stored for future use).	Not available at this time	If resources are available at any site

*This is a suggested minimum follow-up schedule, since ideally in Tier 2; individuals should be followed up to a minimum of a year. Follow-up may be extended beyond this time period as clinically indicated and as resources allow. This is particularly relevant for neurodevelopmental follow-up which would likely involve longer follow-up for 2 years or longer. The suggested follow-up after one year would be at 18 months and 24 months.

** Specific populations refers to: 0- 5 years old, adults and >5 years old, returning traveler, maternal (if no other cohort or case-control studies ongoing in the area), neonate (if no other cohort or case-control studies ongoing in the area).

Depending on the tier in which a participant is enrolled, a structured clinical questionnaire in the form of a case report form (CRF) should be completed as a minimum at the initial visit (i.e. time of enrolment into the study). Participants enrolled in Tier 2 and higher should be assessed daily during the acute illness episode, and ideally, daily follow-up should be continued until the patient has been asymptomatic for 24 hours (i.e. resolution of fever, rash, arthritis/arthralgia etc.). Given some variation in duration of symptoms in each participant, the exact duration may vary. When possible, a

convalescent visit will be scheduled between day 12 – 16. Ideally we suggest medium/long-term follow-up time period up to 12 months past the acute illness episode. Follow up with CRF(s) completion at 3, 6 and 12 months for those site where medium/long term participant follow-up is feasible.

The rapid Zika CRF(s) which includes clinical history and examination, as well as all standard laboratory results based on a minimal data set is called the "Zika Virus Rapid Case Report Form" (see Appendix B) and/or "Zika Virus Rapid Follow-up Case Report Form" (see Appendix C). CRFs may be modified by the primary investigators at participating research sites if required, however for ease of aggregation of data, standardized collection of data without modification to forms is preferred. The minimal data set in the Rapid Zika CRFs is derived from extensively reviewed detailed CRFs available through ISARIC. In settings that allow for the collection of more detailed information or where ongoing ZIKV cohort or case controls on specific populations such as children 0-5, or pregnant women are ongoing, there areother CRFs are available at https://zikainfection.tghn.org/research-tools-and-resources/crfs / and Appendix D and can be used in lieu of the Rapid Zika Virus CRF and allows for more detailed collection of data as described in Table 3.

Collection of biological (laboratory) samples

Laboratory diagnosis of ZIKV will be in accordance with current interim WHO guidelines for the diagnosis of ZIKV infection (http://apps.who.int/iris/bitstream/10665/204671/1/WHO_ZIKV_LAB_16.1_eng.pdf). Any case with positive ZIKV RT-PCR will be defined as having laboratory-confirmed ZIKV infection.

Laboratory diagnosis of DENV will also be in accordance with current WHO criteria. Any case with virological evidence of DENV as shown by an RT-PCR assay or NS1 ELISA test, or who has IgM seroconversion between paired specimens, will be defined as having laboratory-confirmed dengue.

Any case with virological evidence of CHIKV as shown by an RT-PCR assay will be defined as having laboratory-confirmed CHIKV and IgM seroconversion will be viewed as highly suggestive of recent CHIKV infection

Mixed infections (evidence of positive PCR assays for more than one of these viruses) will also be determined.

The schedule for minimal laboratory sampling requested for study purposes, is shown in Table 4. We will carry out testing in an algorithmic approach where appropriate, i.e. in case of a positive PCR, serology does not need to be carried out to classify a confirmed infection. At enrolment and at the convalescent visit a blood sample for biochemical profile (FBC+D, AST, ALT, albumin, creatinine, creatinine-kinase, inflammatory markers (eg. ESR/CRF) if available) will be obtained (if not already done so as part of routine clinical care), together with a blood sample for serology and virological studies. If other laboratory information is collected as part of participant clinical care, this information can be completed in the appropriate population specific laboratory CRFs or in the Rapid Initial or Follow-up Zika Virus CRFs and is also important for the study.

If feasible, banking of a single serum sample from each participant at the time of study enrolment for potential future testing is desirable even if no other lab testing can be performed at the site and may be used for Tier 3 studies in the future.

Table 4: Recommended laboratory sampling during the acute phase of illness and during the convalescent visit

Test	**Sample type**	**Enrolment**	Daily follow-up	Convalescent visit (Day 12-16 post symptom onset)
ZIKV PCR, DENV1-4 PCR, CHIKV PCR ZIKV IgM/G Dengue NS1, Dengue IgM/G, CHIKV IgM/G	Research blood sample to be submitted in whole blood (preferred) but can submit serum if whole blood not available Submit in EDTA	Tier 1 and higher	Not required.	Tier 2 and higher
ZIKV PCR	Research urine sample	Tier 1 and higher	Not required	Not required
Full blood count (FBC) + [differential (D) as available]	Hematology to be submitted in EDTA	Tier 1 and higher	Only if part of routine care in Tier 2 and higher	Tier 2 and higher
AST/ALT, Albumin, Creatine kinase, Creatinine, ESR or CRP	Biochemistry (to be carried out based on local resources) to be submitted in Lithium Heparin*	Tier 1 and higher	Only if part of routine care if Tier 2 and higher	Tier 2 and higher

* or serum / an alternative additive according to local laboratory requirements

Table 5: Information regarding Laboratory samples volumes and storage

Enrolment blood collection	**Patient 0-2 years old**	**Patient age 2-14 years old**	**Patient age >= 15**
	0.5 to 1ml EDTA tube (FBC) 1 to 2ml Lithium Heparin tube (biochemistry) 1.5ml EDTA tube (research)	1ml EDTA tube (FBC) 2ml Lithium Heparin tube (biochemistry) 3ml EDTA tube (research)	1ml EDTA tube (FBC) 2ml Lithium Heparin tube (biochemistry) 5ml EDTA tube (research)
.			

Daily / Follow-up blood Collection (depending on Tier and setting)	Patient 0-2 years old	Patient age 2-14 years old	Patient age >= 15
	For DAILY VISIT (symptomatic period) : 0.5 to 1ml EDTA tube (FBC) **For FINAL ACUTE VISIT (24 hours after symptoms abate):** 0.5 to 1ml EDTA tube (FBC) 1 to 2ml Lithium Heparin tube (biochemistry) 1.5ml EDTA tube (research) **For CONVALESCENT VISIT**: 0.5 to 1ml EDTA tube (FBC) 1.5ml EDTA tube (research)	**For DAILY VISIT (symptomatic period):** 1ml EDTA tube (FBC) **For FINAL ACUTE VISIT (24 hours after symptoms abate)**: 1ml EDTA tube (FBC) 2ml Lithium Heparin tube (biochemistry) 2ml EDTA tube (research) **For CONVALESCENT VISIT**: 1ml EDTA tube (FBC) 2ml EDTA tube (research)	
The Research and Biochemistry samples must be stored at +/-2 or 8°C degrees whilst waiting to be sent to local/reference laboratory If Research samples need to be stored for more than 48 hrs up to 7 days they should be frozen at -20˚C and those samples stored for more than 7 days should be frozen at -70˚C were possible.			

All biological sampling collection will follow WHO for ZIKV testing, however timing of testing will vary based on study follow-up period. See http://apps.who.int/iris/bitstream/10665/204671/1/WHO_ZIKV_LAB_16.1_eng.pdf

2.4.2 DATA MANAGEMENT

All data collected should be stored in a local database compliant with security requirements as dictated by national regulations thereby determined on a study-by-study basis. Local study personnel should double enter anonymized data into local database in a password-protected copy of the database should be de-identified (without name, address) and sent for data analysis to the designated data manager(s

Data protection regulations will be strictly adhered to. Participants' identities will be protected and their information will be held securely and only aggregate summary data released publically. Original data collection forms will be kept in locked storage in accordance with national regulations for 15

years after the end of the study. An identification log will be implemented and will be kept in a secure, locked facility within the study country.

The creation of a unified and centralized electronic database corresponding to the information recorded in the CRF(s) is not available at this time. If a central data management system becomes available in the future a fundamental principle of this work is that clinical investigators contributing to research efforts, often in extremely difficult circumstances, must be given full recognition for their efforts and the opportunity to access data and samples. Ownership of any data transferred to the centralized database will be retained by the site that contributed it. However, the power of a standardized protocol such as this one comes from the ability to pool data across various sites and settings for analysis. All analysis of pooled data will be undertaken with the explicit agreement of each site that has contributed data.

2.4.3 COMPENSATION AND INCENTIVES TO PARTICIPATE

Participants can be offered reimbursement for reasonable out of pocket expenses; however, the level of compensation should not be such that participants are unduly influenced into consenting to participate. It should be determined on a study-by study-basis, in alignment to country/local guidelines. WHO is not responsible for this reimbursement.

2.4 SPECIMEN COLLECTION AND LABORATORY INVESTIGATIONS

2.4.1 SPECIMEN COLLECTION, STORAGE AND TRANSPORTATION

Specimen transportation within national borders should comply with national regulations. For the transport of samples/specimens internationally, compliance with International Health Regulations (IHR) is required. See http://apps.who.int/iris/bitstream/10665/78075/1/WHO_HSE_GCR_2012.12_eng.pdf for more information. These specimens should be marked as Category B.

Samples will be collected according to the availability of local resources and the weight of the patient, to prevent excessive volume sampling from children and small adults (see Table 4). The frequency of sample collection will be determined by the tier in which the participant is enrolled.

Hematology and biochemistry analysis will be performed on standard instruments at each participating site.

Diagnostic serological assays will be performed by investigators at each clinical site if available, otherwise may need to be referred to the reference lab. WHO will provide guidance on assay selection and assist in identifying local laboratories that can perform the required testing.

Where feasible, PCR should be performed in reference laboratories with quality control measures implemented. This should be coordinated by the local study investigator. WHO can provide lab matching to sites requesting this service. Wherever possible, technology transfer will be carried out to allow centers to acquire new assays. Harmonization of assay protocols, reagents and equipment should be performed prior to testing of clinical specimens across the study sites.

For DENV, different commercially available NS1 ELISA assays as well as IgM and IgG assays are available. [***insert name of available assay for this purpose at site***]. NS1 detection will be attempted on enrolment plasma samples. [***Insert name and outline role of participating laboratory in your country/region***]

Determination regarding the provision of test results to the treating physician and/or patient may be made by the local investigators in the context of local resource availability and laboratory testing turn-around times.

If feasible, banking of a single serum sample from each participant at the time of study enrolment for potential future testing is desirable even if no other lab testing can be performed at the site.

We are requesting consent to having blood samples stored, to export samples, and to have genetic studies performed on the study participants. All stored and exported samples will be pseudo-anonymized using a study identification number and linked to protected identifying information at the study site only. No identifying data will be exported or shared. These genetic studies are exploratory and we do not yet know whether the results will be helpful in treating patients with this disease.

3.0 STUDY ENDPOINTS AND STATISTICAL ANALYSES

3.1 SAMPLE SIZE CONSIDERATIONS

As this is an observational descriptive study of an emerging pathogen sample size does not apply. This protocol is not hypothesis based however, it can be used to create hypothesis upon gathering of clinical information.

3.2 STUDY OUTCOME MEASURES AND STATISTICAL ANALYSES

There are no specific outcomes measures other than confirmed ZIKV infection itself. If severe manifestations are identified as part of the clinical spectrum, they could potentially be further characterized as outcomes.

Descriptive data analysis should be conducted per tier and results stratified by age group and presence of underlying comorbidities. Heterogeneity between countries and recruiting sites should be assessed prior to pooling datasets in multicenter analysis.

Participants in tier 0 or 1 can be analyzed in real-time as clinical information becomes available. For participants in tier 2 data analysis can occur at several time points: after the acute illness, after the convalescent visit, and at each of the follow up points of 3, 6 and 12 months, with the possible extension of analysis at 18 and 24 months if the study involves following the study participants for this long. Tier 3 involves the same analysis points as Tier 2 and may involves further analysis to be determined at a later time point.

We hope to assess a broad range of clinical and laboratory parameters in order to develop a clinical case definition for ZIKV infection in the context of other circulating arboviruses (e.g. DENV and CHIKV). This will be carried out using multivariable regression techniques. Covariates assessed will include symptoms at presentation, examination findings, and readily available laboratory parameters. Amongst participants with confirmed ZIKV, the objective is to identify simple clinical and laboratory parameters correlating with confirmed infection and to compare the results with the interim case definition from WHO.

Should complications be identified as part of the clinical spectrum, risk factors associated with these complications will be analyzed using multivariable regression techniques.

4.0 REPORTING OF FINDINGS

The WHO supports the conduct of investigator-led clinical research in outbreaks of emerging infections. Studies using this protocol will be compatible with other studies, enabling future collaboration or data synthesis. Investigators utilizing this protocol are therefore requested to inform the WHO of this. Investigators are encouraged to share data with the WHO or its collaborators though there is no obligation to do so. Any deviations of the study methodologies should also be reported to WHO in order to aid in the interpretation of findings and possible aggregation across sites. Though pooled data analysis may be performed with the permission of local investigators, ownership of the data remains with the contributing site and all contributing sites will be acknowledged in any resulting publications.

5.0 TIMELINE

The study will start in [***insert month/year***] in [***insert name of country / region***] at [*** insert name of first participating site***].

Data entry, validation, and query resolution will run in parallel with recruitment. The development of a centralized data management system is currently in progress.

6.0 COMPLEMENTARY STUDIES

The following complementary study protocols listed below are available via the following link http://www.who.int/reproductivehealth/zika/zika-virus-research-agenda/en/:

- Case-control study to assess potential risk factors related to microcephaly including Zika virus infection during pregnancy
- Prospective longitudinal study of newborns and infants born to mothers exposed to Zika virus during pregnancy
- Prospective longitudinal cohort study of women and newborns exposed to Zika virus during the course of pregnancy
- Prospective longitudinal cohort study of Zika-infected patients to measure the persistence of Zika virus in bodily fluids
- Case-control study to assess potential risk factors related to Guillain-Barre Syndrome including Zika virus infection
- Cross-sectional seroprevalence study of Zika virus infection in the general population

7.0 ADDITIONAL ACKNOLWEDGEMENTS

A large number of individuals were involved in the creation and revision of this protocol and research tools (CRFs, completion guidelines, data dictionaries). These include:

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APPENDICES

APPENDIX A – COUNTRY CONTEXT [***For the country to insert - information about the epidemiology of the outbreak in the country/region conducting this study***]

APPENDIX B - ZIKA VIRUS INITIAL CASE REPORT FORM: Rapid Form

APPENDIX C - ZIKA VIRUS FOLLOW-UP CASE REPORT FORM: Rapid Form

APPENDIX D – POPULATION SPECIFIC CASE REPORT FORMS

APPENDIX E – CONSENT AND ASSENT FORMS

APPENDIX A: COUNTRY CONTEXT

ZIKA VIRUS INITIAL CASE REPORT FORM: RAPID FORM

Participant's identification code: _____

DESIGN OF THIS CASE REPORT FORM (CRF)

This case report form (CRF) is designed to be used as a tool for the rapid collection of a minimal data set for the initial presentation of the participant in the outpatient, district or tertiary hospital setting. Since one form is available for all age groups, certain parameters may not be relevant for individual participants. Follow-up case report forms are also available to be completed daily during the period that the participant remains symptomatic and intermittently for a follow-up period afterwards.

HOW TO USE THIS CRF

When completing the CRF please ensure that:

- The participant or consultee/guardian/representative has been given information about the observational study and the informed consent form has been completed and signed.
- The study ID codes will be assigned for the participant.
- The study ID codes should be filled in on all pages of paper CRF forms, all information should be kept confidential at all times, and no participant identifiable information is recorded on the CRFs.
- Participants' hospital ID and contact details should be recorded on a separate contact list to allow later follow up. The contact forms must be kept separate from the CRFs at all times and kept in a secure location.

Each site may choose which data to collect based on available resources and the number of patients enrolled to date. The decision is up to the site Investigators and may be changed throughout the data collection period. All high quality data is valuable for analysis.

GENERAL GUIDANCE

- **This CRF is designed to collect a minimal data set obtained through gathering clinical information including participant interview, physical examination, and review of clinical notes.**
- Researchers/clinicians may add more questions to this document which is meant to collect the minimal amount of data required to help elucidate the natural history of this infection.
- **For researchers/clinicians who are looking for more detailed and specific CRFs these are available through ISARICs website: https://zikainfection.tghn.org/research-tools-and-resources/crfs/**
- Complete every line of every section, except for where the instructions say to skip a section based on certain responses. Please mark the 'Unknown' box if the answer to a particular question is not known.
- Selections with square boxes (☐) are single selection answers (choose one answer only). Selections with circles (○) are multiple selection answers (choose as many answers as are applicable).
- Some sections have open areas where you can write additional information. To permit standardized data entry, please avoid writing additional information outside of these areas.
- We recommend writing clearly in black or blue ink, using BLOCK-CAPITAL LETTERS.
- Place an (X) when you choose the corresponding answer. To make corrections, strike through (----) the data you wish to delete and write the correct data above it. Please initial and date all corrections.
- Please contact us if we can help with any CRF completion questions, if you have comments and to let us know that you are using the forms. Please contact Dr Nahoko Shindo by email: shindon@who.int or Dr Gail Carson by email gail.carson@ndm.ox.ac.uk

ZIKA VIRUS INITIAL CASE REPORT FORM: RAPID FORM

Participant's identification code: _____

VERIFICATION OF ELIGIBILITY

INCLUSION CRITERIA	Yes	No
Individuals of all ages who provides written informed consent/assent	☐	☐
EXCLUSION CRITERIA	**Yes**	**No**
Contraindication to venepuncture	☐	☐
Unable to obtain written informed consent/assent	☐	☐

Who is providing the information (eg. participant, parent, other relative, caregiver etc.)?	☐Participant ☐Other (Relationship to patient (e.g. mother: _____) ☐Chart review

DEMOGRAPHICS

1. Date (DD/MM/YYYY):	__ / __ / 20 __
2. Name of site/outpatient clinic:	
3. City/town/village:	
4. State:	
5. Country:	
6. Main home address:	
7. Location of residence	☐City/Urban ☐Rural/countryside ☐Other (specify):
8. Date of Birth (DD/MM/YYYY):	__ / __ / ____
9. Date of onset of first symptoms (DD/MM/YYYY):	__ / __ / 20 ____
10. Sex:	☐Male ☐Female
11. Weight	_____ ☐ kg ☐ pounds/ounces
12. Height	_____ ☐ cm ☐ inches
13. Ethnicity (use local classifications)	
14. Pregnant **If yes, give Gestational Age**	☐Yes Gestational age. __ weeks __ days ☐No ☐Unknown ☐Not applicable
15. Occupation:	☐Describe: _____ ☐Unknown ☐Not applicable

SYMPTOMS AND/OR SIGNS (since first day of onset of this illness episode)

16. Confusion/disorientation	☐Yes ☐No ☐Unknown
17. Amnesia	☐Yes ☐No ☐Unknown
18. Altered behaviour or personality	☐Yes ☐No ☐Unknown
19. Depression	☐Yes ☐No ☐Unknown
20. Mood/behavioural concerns	☐Yes ☐No ☐Unknown

ZIKA VIRUS INITIAL CASE REPORT FORM: RAPID FORM

Participant's identification code: _____

If yes, please describe:		
21. Headache	☐Mild ☐Moderate ☐Severe ☐No ☐Unknown	
22. Periorbital pain	☐Yes ☐No ☐Unknown	
23. Photophobia	☐Yes ☐No ☐Unknown	
24. Neck stiffness	☐Yes ☐No ☐Unknown	
25. Seizures	☐General ☐Focal ☐No ☐Unknown	
26. Paralysis	☐General ☐Ascending ☐No ☐Unknown	
If yes, please describe affected body parts and if progressive:		
27. Weakness	☐General ☐Focal ☐No ☐Unknown ○Power test (ie.confirmed by physical exam) ○Patient complaint	
If focal, please describe affected body parts and if progressive:		
28. Numbness/tingling in extremities	☐Yes ☐No ☐Unknown	
29. Movement disorder	☐Yes ☐No ☐Unknown	
30. Oromotor dysfunction	☐Yes ☐No ☐Unknown	
31. Sore throat	☐Yes ☐No ☐Unknown	
32. Cough	☐Yes ☐No ☐Unknown	
33. Conjunctivitis	☐Yes ☐No ☐Unknown	
If yes, specify if:	☐Purulent ☐Non-purulent	
34. Mouth ulcers	☐Yes ☐No ☐Unknown	
35. Shortness of breath	☐Yes ☐No ☐Unknown	
36. Chest pain	☐Yes ☐No ☐Unknown	
37. Diarrhoea	☐Yes ☐No ☐Unknown	
38. Vomiting/nausea	☐Yes ☐No ☐Unknown	
39. Stomach pain	☐Yes ☐No ☐Unknown	
40. Back pain	☐Yes ☐No ☐Unknown	
41. Myalgia	☐Yes ☐No ☐Unknown	
42. Arthralgia	☐Yes ☐No ☐Unknown	
43. Joint swelling	☐Yes ☐No ☐Unknown	
If yes, specify all affected joints:	○Fingers ○Toes ○Knee ○Elbow ○Other ☐ yes ☐ no if yes specify:_____	
44. Rash	☐Yes ☐No ☐Unknown	
If yes, please check box for type of rash and specify location:		**Spread of the rash:**
45. Maculopapular rash	☐Yes ☐No	☐Centrifugal ☐Centripetal
46. Erythematous rash	☐Yes ☐No	☐Centrifugal ☐Centripetal
47. Non blanching rash	☐Yes ☐No	☐Centrifugal ☐Centripetal
48. Vesicular rash	☐Yes ☐No	☐Centrifugal ☐Centripetal
49. Pruritic rash	☐Yes ☐No	☐Centrifugal ☐Centripetal
50. Petechial or purpuric rash	☐Yes ☐No	☐Centrifugal ☐Centripetal
51. Bruising/ ecchymosis	☐Yes ☐No	☐Centrifugal ☐Centripetal
52. If other type of rash, please specify:	Type: ○ face ○ torso ○ upper limbs ○ lower limbs ○ palms ○ other:	
53. Sign of insect bites	☐Yes ☐No ☐Unknown	
54. Jaundice	☐Yes ☐No ☐Unknown	
55. Bleeding	☐Yes ☐No ☐Unknown	
If yes, please state source (e.g. urine, stool):		

ZIKA VIRUS INITIAL CASE REPORT FORM: RAPID FORM

Participant's identification code: _____

BASELINE OBSERVATIONS AND SIGNS AT PRESENTATION (initial presentation)

56. Maximum Temperature	___°C ☐Oral ☐Tympanic ☐Axillary ☐Anal ☐Skin	
57. Respiratory Rate	_____breaths/minute ☐ Unknown	
58. Heart Rate	_____ beats/minute ☐ Unknown	
59. Systolic Blood Pressure	_____mmHg ☐ Unknown	
60. Diastolic Blood Pressure	_____mmHg ☐ Unknown	
61. Peripheral O_2 Saturation (SpO_2)	_____ % ☐Not recorded ☐ Unknown	
62. Glasgow Coma Score (out of 15)	___ / 15 OR ☐NA	
63. AVPU	☐A ☐V ☐P ☐U OR ☐NA	
64. Lymphadenopathy	☐Cervical only ☐General ☐No ☐Unknown	
65. Fundoscopy	Describe findings:	
66. Cardiovascular system	☐Normal ☐Abnormal ☐ Unknown	If abnormal, specify: ☐Murmur ☐Other:
67. Respiratory system	☐Normal ☐Abnormal ☐Unknown	If abnormal, describe:
68. Gastrointestinal system	☐Normal ☐Abnormal ☐Unknown	☐ Jaundice ☐ Abdominal tenderness ☐ Hepatomegaly ☐ Splenomegaly ☐ Hernia ☐ Omphaloceles ☐ Gastroschesis ☐Other (specify): _____
69. Neurological system	☐Normal ☐Abnormal ☐Unknown	☐ Paralysis – general ☐ Paralysis – ascending ☐ Paralysis – descending ☐ Hypotonia ☐ Weakness ☐ Arthrogryposis ☐ Stiffness or spasticity ☐ Abnormal movements (describe):_____ ☐Other (specify): _____
70. Rash	☐Yes ☐No ☐Unknown	If yes, describe type of rash, body distribution: If yes, date of rash onset **(**DD/MM/YYY**):** **____/_____/20_____**
71. Dysmorphisms	☐Yes ☐No ☐Unknown	☐ Eye abnormalities ☐ Skull deformities ☐ Ear abnormalities ☐ Limb abnormalities ☐Other (specify):

ZIKA VIRUS INITIAL CASE REPORT FORM: RAPID FORM

Participant's identification code: _____

PRE-EXISTING MEDICAL CONDITIONS

72. Chronic cardiovascular disease[1]	☐Yes ☐No ☐Unknown
73. Chronic pulmonary disease[2]	☐Yes ☐No ☐Unknown
74. Blood disorders	☐Yes ☐No ☐Unknown
If yes, specify:	
75. Chronic renal/kidney disease[3]	☐Yes ☐No ☐Unknown
76. Chronic liver disease – moderate or severe[4]	☐Yes ☐No ☐Unknown
77. Chronic neurological disease[5]	☐Yes ☐No ☐Unknown
If yes, specify:	
78. Paralysis	☐Yes ☐No ☐Unknown
If yes, specify cause and body parts affected:	
79. Type 1 Diabetes	☐Yes ☐No ☐Unknown
80. Type 2 Diabetes and treated with oral medicine or insulin dependent	☐Yes ☐No ☐Unknown
81. Other endocrine disease[6]	☐Yes ☐No ☐Unknown
82. Rheumatologic disease[7]	☐Yes ☐No ☐Unknown
83. Immunosuppression	☐Yes ☐No ☐Unknown
84. HIV[8]	☐Yes ☐No ☐Unknown
If yes, on antiretroviral therapy?	☐Yes ☐No ☐Unknown

[1] Includes coronary heart disease, cerebrovascular disease (stroke), hypertension (Diastolic > 100), peripheral artery disease, rheumatic heart disease, congenital heart disease and heart failure. www.who.int/topics/cardiovascular_diseases/en/

[2] Chronic lung diseases that cause limitations in lung airflow (previously referred to as emphysema, chronic bronchitis), diagnosed by spirometry or clinical signs e.g. abnormal shortness of breath and increased forced expiratory time. www.who.int/respiratory/copd/diagnosis/en/

[3] Creatinine >3mg% (265 umol/l), dialysis, transplantation, uremic syndrome

4 Cirrhosis with PHT +/- variceal bleeding

5 Disorders of the nervous system e.g. epilepsy, MS, Parkinson, chronic pain syndromes, chronic brain injuries, ALS etc.

6 Hypopituarism, adrenal insufficiency, recurrent acidosis

7 SLE, polymyositis, polymyalgia rheumatic, mixed connective tissue diseases

8 Laboratory-confirmed HIV-1 or HIV-2 infection (irrespective of the CD4 lymphocyte count/percentage or HIV viral load in blood), or a patient with an AIDS-defining condition.

ZIKA VIRUS INITIAL CASE REPORT FORM: RAPID FORM

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85. CD4 cell count (most recent)	☐ <200 cells/µL ☐200-499 cells/µL ☐ ≥500 cells/µL ☐Unknown
86. Other immunosuppression?	☐Yes ☐No ☐Unknown
If yes, specify:	
87. Any other chronic comorbidity	☐Yes ☐No ☐Unknown
If yes, specify:	
88. Past infection of Dengue/Dengue Hemorrhagic Fever	☐Yes ☐No ☐Unknown
If yes, specify when:	
89. Past infection of Chikungunya	☐Yes ☐No ☐Unknown
If yes, specify when:	
90. Past infection of Yellow Fever	☐Yes ☐No ☐Unknown
If yes, specify when:	

INFANT HISTORY (complete for children < 5 years old)

If infant history is not applicable please tick here: ☐ and proceed to section on medications administered.

91. Term gestation (37-42 weeks gestational age): ☐Yes ☐No, specify GA _____ wks ☐Unknown
92. Mode of delivery: ☐Vaginal delivery ☐Cesarean section ☐Unknown
93. Birth weight: _____ ☐kg ☐ lbs+oz ☐ Estimated ☐ Measured
94. Birth length: _____ ☐cm ☐inches
95. Head circumference* : _____ ☐cm ☐inches **Percentile :** _____
96. Resuscitation required at birth: ☐Yes If yes: ☐ Suction ☐ Oxygen ☐ Positive pressure ventilation (PPV) ☐ Intubation ☐No ☐Unknown

97. Currently breastfeeding:

☐Yes ☐No ☐Unknown

***If neonate, head circumference measurement to be taken 12 hours after birth and not later than 24 hours**

MEDICATIONS ADMINISTERED (from onset of first symptoms of this illness episode)

List all medications administered for acute symptoms:
Use generic names, list all treatment given to the mother for this illness episode from date of onset.

Type of medication	**Name of medication** (generic name)	**Start date** (dd/mm/yyyy)	**Number of days duration**	**Route of administration**
98. Antibiotics ☐Yes ☐No				☐IV ☐Oral
				☐IV ☐Oral
99. Antivirals ☐Yes ☐No				☐IV ☐Oral
				☐IV ☐Oral
100. Corticosteroids ☐Yes ☐No				☐IV ☐Oral ☐Topical ☐Inhaled
101. Anticonvulsants ☐Yes ☐No				☐IV ☐Oral
102. Anti-inflammatory (e.g. NSAIDs) ☐Yes ☐No				☐IV ☐Oral
103. Immunoglobulins ☐Yes ☐No				☐IV ☐Oral
104. Other (specify):				☐IV ☐Oral
Other (specify):				☐IV ☐Oral
Other (specify):				☐IV ☐Oral
Other (specify):				☐IV ☐Oral

EXPOSURES

105. Tobacco use?	☐Yes ☐No ☐Unknown	**If yes, specify average per day:**	☐ <10 cigarettes per day ☐ ≥10 cigarettes per day
106. Alcohol consumption?	☐Yes ☐No ☐Unknown	**If yes, specify average alcohol consumption per day**	☐ Less than 1-2 alcoholic drinks[9] per day ☐ 2-5 alcoholic drinks per day ☐ >5 alcoholic drinks per day
107. Illicit and recreational drug use ?	☐Yes ☐No ☐ Unknown	**If yes, specify all types of drugs used and route of administration:**	

[9] A drink is defined as any alcoholic drink for example a glass of wine, a glass of beer, a cocktail

ZIKA VIRUS INITIAL CASE REPORT FORM: RAPID FORM

Participant's identification code: _____

108. Has you ever received a blood transfusion?	☐Yes ☐No ☐Unknown	**Specify/estimate date of last blood transfusion:** ☐< 30 days ago ☐>30 days ago	**Reason for transfusion:**
109. Has anyone you know had Zika infection? **If yes (give date of presentation to clinic):** ○ **Partner** ○ **Children** ○ **Parent** ○ **Neighbors** ○ **Close friend/relative** ○ **Other (specify): _____**	☐ Yes ☐ No ☐ Unknown ☐ Yes ☐ No ☐ Unknown ☐ Yes ☐ No ☐ Unknown ☐ Yes ☐ No ☐ Unknown ☐ Yes ☐ No ☐ Unknown ☐ Yes ☐ No ☐ Unknown ☐ Yes ☐ No ☐ Unknown		Date of presentation to clinic: __ / __ / _____ __ / __ / _____ __ / __ / _____ __ / __ / _____ __ / __ / _____ __ / __ / _____
110. Have you had sexual contact with anyone who has recently travelled to a Zika infected area (i.e. within the last 6 months)	☐Yes ☐No ☐Unknown ☐Does not wish to answer		
111. Within the last 4 weeks: please specify types of sexual activity undertaken (tick all that apply)	○ Oral ○ Vaginal ○ Anal ○ Other (specify): _____ ○ Does not wish to say		
112. Within the last 4 weeks: please specify types of protection used (tick all that apply)	○ None ○ Condoms (male/female) ○ Diaphragm/Cap ○ Dental dam ○ Gloves ○ Other (specify): _____ ○ Does not wish to say		
113. Any history of travel (local/national/international) ☐ **Yes** ☐ **No**	**Approximate first and last date [DD/MM/YYYY]** __/__/____ to __/__/____ __/__/____ to __/__/____ __/__/____ to __/__/____ __/__/____ to __/__/____	**If yes: places visited**	
114. Vector Control	○ Insecticides for Larvae If yes, ☐ Daily ☐ Sometimes ☐ Often		

	○ Removing Standing Water from Around House If yes, ☐ Daily ☐ Sometimes ☐ Often ○ Insecticide Fogging If yes, ☐ Daily ☐ Sometimes ☐ Often ○ Other (specify): _____ If yes, ☐ Daily ☐ Sometimes ☐ Often

IMMUNIZATION HISTORY

Vaccine	Immunized	Date of last dose (dd/mm/yyyy)
115. Rubella	☐Yes ☐No ☐Unknown	
116. Measles	☐Yes ☐No ☐Unknown	
117. Mumps	☐Yes ☐No ☐Unknown	
118. Acellular pertussis	☐Yes ☐No ☐Unknown	
119. Varicella	☐Yes ☐No ☐Unknown	
120. Tetanus	☐Yes ☐No ☐Unknown	
121. Diphtheria	☐Yes ☐No ☐Unknown	
122. Polio	☐Yes ☐No ☐Unknown	
123. Seasonal influenza	☐Yes ☐No ☐Unknown	
124. Yellow fever	☐Yes ☐No ☐Unknown	
125. Japanese encephalitis	☐Yes ☐No ☐Unknown	
126. Tick-born encephalitis	☐Yes ☐No ☐Unknown	
127. Dengue virus	☐Yes ☐No ☐Unknown	
128. Any other vaccinations (specify):	☐Yes ☐No ☐Unknown If yes, please specify immunization type:	
Any other vaccinations (specify):	☐Yes ☐No ☐Unknown If yes, please specify immunization type:	

ZIKA VIRUS INITIAL CASE REPORT FORM: RAPID FORM

Participant's identification code: _____

LABORATORY RESULTS

Record all values available ≤24 hours of presentation/admission as part of the clinical care of patient included in the study. Please use standard (SI) units if possible. Please specify the unit used for each result. For repeat testing, use the most abnormal value per day copy page and ensure date of testing and patient IDs are indicated on each page.

If no laboratory results are available please tick here: ☐ and proceed to section on microbiological tests

Date of sampling (DD/MM/YYYY):	**__ / __ / 20 __**		
Test		**Value**	**Specify unit, if other specify unit used.**
Inflammatory markers			
129. C-reactive protein	☐Yes ☐Not done ☐Unknown		☐mg/L ☐other:_____
130. Erythrocyte sedimentation rate	☐Yes ☐Not done ☐Unknown		☐mm/hr ☐other:_____
131. Procalcitonin	☐Yes ☐Not done ☐Unknown		☐ng/mL ☐other:_____
Haematology			
132. Haemoglobin	☐Yes ☐Not done ☐Unknown		☐g/L ☐g/dL ☐other:_____
133. Haematocrit	☐Yes ☐Not done ☐Unknown		☐% ☐other:_____
134. RBC count	☐Yes ☐Not done ☐Unknown		☐x10^9/L *or* ☐x10^3/µL ☐other:_____
135. MCV	☐Yes ☐Not done ☐Unknown		☐µm^3 ☐other:_____
136. White blood cell count	☐Yes ☐Not done ☐Unknown		☐x10^9/L ☐x10^3/µL ☐other:_____
137. Neutrophils	☐Yes ☐Not done ☐Unknown		☐**10^3/mm^3** ☐**%** ☐other:_____
138. Lymphocytes	☐Yes ☐Not done ☐Unknown		☐**10^3/mm^3** ☐**%** ☐other:_____
139. Monocytes	☐Yes ☐Not done ☐Unknown		☐**10^3/mm^3** ☐**%** ☐other:_____
140. Eosinophils	☐Yes ☐Not done ☐Unknown		☐**10^3/mm^3** ☐**%** ☐other:_____
141. Basophils	☐Yes ☐Not done ☐Unknown		☐**10^3/mm^3** ☐**%** ☐other:_____
142. Platelets	☐Yes ☐Not done ☐Unknown		☐x10^9/L *or* ☐x10^3/µL ☐other:_____
143. APTT	☐Yes ☐Not done ☐Unknown		☐seconds
144. PT (seconds)	☐Yes ☐Not done ☐Unknown		☐seconds
145. Blood film	☐Yes ☐Not done ☐Unknown		Describe results:
Biochemistry			
146. Urea nitrogen	☐Yes ☐Not done ☐Unknown		☐mmol/L ☐mg/dL ☐other:_____
147. Creatinine	☐Yes ☐Not done ☐Unknown		☐µmol/L ☐mg/dL ☐other:_____
148. Sodium	☐Yes ☐Not done ☐Unknown		☐mmol/L ☐other:_____
149. Potassium	☐Yes ☐Not done ☐Unknown		☐ mmol/L ☐other:_____
150. Total protein	☐Yes ☐Not done ☐Unknown		☐g/dL ☐other:_____
151. Albumin	☐Yes ☐Not done ☐Unknown		☐g/L ☐other:_____
152. Bilirubin	☐Yes ☐Not done ☐Unknown		☐µmol/L ☐mg/dL ☐other:_____
153. AST/SGOT	☐Yes ☐Not done ☐Unknown		☐U/L ☐other:_____
154. ALT/SGPT	☐Yes ☐Not done ☐Unknown		☐U/L ☐other:_____
155. GGT	☐Yes ☐Not done ☐Unknown		☐U/L ☐other:_____
156. ALP	☐Yes ☐Not done ☐Unknown		☐U/L ☐other:_____
157. Calcium	☐Yes ☐Not done ☐Unknown		☐mmol/L ☐other:_____
158. Phosphate	☐Yes ☐Not done ☐Unknown		☐mg/dL ☐other:_____
159. Magnesium	☐Yes ☐Not done ☐Unknown		☐mmol/L ☐other:_____

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Participant's identification code: _____

160. Amylase	☐Yes ☐Not done ☐Unknown		☐U/L ☐other:_____
161. Glucose	☐Yes ☐Not done ☐Unknown		☐mmol/L ☐mg/dL ☐other:_____
162. Creatine kinase	☐Yes ☐Not done ☐Unknown		☐U/L ☐other:_____
163. Other biochemistry result (specify):	☐Yes ☐Not done ☐Unknown		☐Unit:_____
Other biochemistry result (specify):	☐Yes ☐Not done ☐Unknown		☐Unit:_____
If yes , describe results:			
164. Lumbar puncture	☐Yes ☐Not done ☐Unknown		

MICROBIOLOGICAL TESTS Record final diagnostics outcomes based on laboratory results, clinical picture and case definitions. Choose the appropriate case definition, e.g WHO or national/local case definition and ensure the definition used is clear and shared with all involved in the study.

If no microbiological results are available please tick here: ☐ and proceed to section on imaging

Pathogen	Diagnosis	Date of onset (DD/MM/YYYY)	Comment
165. Zika virus	☐ Confirmed acute infection ☐Probable acute infection ☐Confirmed past infection ☐Probable past infection ☐Negative ☐Not tested ☐ Unknown	__ / ____ / 20 ___	
166. Dengue virus	☐ Confirmed acute infection ☐Probable acute infection ☐Confirmed past infection ☐Probable past infection ☐Negative ☐Not tested ☐ Unknown	__ / ____ / 20 ___	
167. Yellow fever virus	☐ Confirmed acute infection ☐Probable acute infection ☐Confirmed past infection ☐Probable past infection ☐Negative ☐Not tested ☐ Unknown	__ / ____ / 20 ___	

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168. West Nile virus	☐ Confirmed acute infection ☐Probable acute infection ☐Confirmed past infection ☐Probable past infection ☐Negative ☐Not tested ☐ Unknown	__ / ____ / 20 ___	
169. Chikunguny a virus	☐ Confirmed acute infection ☐Probable acute infection ☐Confirmed past infection ☐Probable past infection ☐Negative ☐Not tested ☐ Unknown	__ / ____ / 20 ___	
170. Toxoplasmo sis	☐ Confirmed acute infection ☐Probable acute infection ☐Confirmed past infection ☐Probable past infection ☐Negative ☐Not tested ☐ Unknown	__ / ____ / 20 ___	
171. Rubella	☐ Confirmed acute infection ☐Probable acute infection ☐Confirmed past infection ☐Probable past infection ☐Negative ☐Not tested ☐ Unknown	__ / ____ / 20 ___	
172. Cytomegalo virus	☐ Confirmed acute infection ☐Probable acute infection ☐Confirmed past infection ☐Probable past infection ☐Negative ☐Not tested ☐ Unknown	__ / ____ / 20 ___	
173. Herpes Simplex virus	☐ Confirmed acute infection ☐Probable acute infection ☐Confirmed past infection ☐Probable past infection ☐Negative ☐Not tested ☐ Unknown	__ / ____ / 20 ___	
174. Syphilis	☐ Confirmed acute infection ☐Probable acute infection ☐Confirmed past infection ☐Probable past infection ☐Negative ☐Not tested ☐ Unknown	__ / ____ / 20 ___	

175. Other (specify):	☐ Confirmed acute infection ☐Probable acute infection ☐Confirmed past infection ☐Probable past infection ☐Negative	__ / ____ / 20 ___	
Other (specify):	☐ Confirmed acute infection ☐Probable acute infection ☐Confirmed past infection ☐Probable past infection ☐Negative	__ / ____ / 20 ___	

IMAGING

If no microbiological results are available please tick here: ☐ and proceed to section on outcome

Imaging	**Results**	**If abnormal, please summarize key results:**	**Images attached**	**Report attached**
176. Cranial ultrasound scan	☐Normal ☐Abnormal ☐Not Done		☐Yes ☐No	☐Yes ☐No
177. MRI brain (record only if done as part of routine care)	☐Normal ☐Abnormal		☐Yes ☐No	☐Yes ☐No
178. CT brain (record only if part of routine care)	☐Normal ☐Abnormal		☐Yes ☐No	☐Yes ☐No
179. Other (specify type of test):	☐Normal ☐Abnormal		☐Yes ☐No	☐Yes ☐No
Other (specify type of test):	☐Normal ☐Abnormal		☐Yes ☐No	☐Yes ☐No

OUTCOME

180. Was the patient discharged home?	☐Yes ☐No ☐Unknown
181. Was the patient transferred to another facility/hospital?	☐Yes ☐No ☐Unknown

ZIKA VIRUS INITIAL CASE REPORT FORM: RAPID FORM

Participant's identification code: _____

	If yes: ☐ICU ☐Ward ☐Emergency Department
182. If yes, please state name of the facility and city (address if possible):	
183. Please state reason for transfer:	
184. Did the patient die?	☐Yes ☐No ☐Unknown
If yes, please attach autopsy result if available:	

CASE REPORT FORM COMPLETED BY

Name and role			
Signature		**Date** (DD/MM/YYY)	

ZIKA VIRUS FOLLOW-UP CASE REPORT FORM: RAPID FORM

Participant's identification code: _____

DESIGN OF THIS CASE REPORT FORM (CRF)

This case report form (CRF) is designed to be used as a minimal data set for the follow-up of the participant in in the outpatient, district or tertiary hospital setting. Since one form is available for all age groups, certain parameters may not be relevant for individual participants. Follow-up case report forms are also available to be completed daily during the period that the participant remains symptomatic and intermittently for a follow-up period afterwards.

HOW TO USE THIS CRF

When completing the CRF please ensure that:

- The participant or consultee/guardian/representative has been given information about the observational study and the informed consent form has been completed and signed.
- The study ID codes will be assigned for the participant.
- The study ID codes should be filled in on all pages of paper CRF forms, all information should be kept confidential at all times, and no participant identifiable information is recorded on the CRFs.
- Participants' hospital ID and contact details should be recorded on a separate contact list to allow later follow up. The contact forms must be kept separate from the CRFs at all times and kept in a secure location.

Each site may choose the amount of data to collect based on available resources and the number of patients enrolled to date. The decision is up to the site Investigators and may be changed throughout the data collection period. All high quality data is valuable for analysis.

GENERAL GUIDANCE

- **This CRF is designed to collect a minimal data set obtained through gathering clinical information including participant interview, physical examination, and review of clinical notes.**
- Researchers/clinicians may add more questions to this document which is meant to collect the minimal amount of data required to help elucidate the natural history of this infection.
- **For researchers/clinicians who are looking for more detailed and specific CRFs these are available through ISARICs website: https://zikainfection.tghn.org/research-tools-and-resources/crfs/**
- Complete every line of every section, except for where the instructions say to skip a section based on certain responses. Please mark the 'Unknown' box if the answer to a particular question is not known.
- Selections with square boxes (☐) are single selection answers (choose one answer only). Selections with circles (○) are multiple selection answers (choose as many answers as are applicable).
- Some sections have open areas where you can write additional information. To permit standardized data entry, please avoid writing additional information outside of these areas.
- We recommend writing clearly in black or blue ink, using BLOCK-CAPITAL LETTERS.
- Place an (X) when you choose the corresponding answer. To make corrections, strike through (----) the data you wish to delete and write the correct data above it. Please initial and date all corrections.
- Please contact us if we can help with any CRF completion questions, if you have comments and to let us know that you are using the forms. Please contact Dr Nahoko Shindo by email: shindon@who.int and/or Dr Gail Carson by email gail.carson@ndm.ox.ac.uk

ZIKA VIRUS FOLLOW-UP CASE REPORT FORM: RAPID FORM

Participant's identification code: _____

Who is providing the information (eg. participant, parent, other relative, caregiver etc.)?	□Participant □Other (Relationship to patient (e.g. mother: _____) □Chart review

1. Date of form completion (DD/MM/YYYY):	__ / __ / 20 __

NEW SYMPTOMS (since completion of INITIAL case report form)

2. Confusion/disorientation	☐Yes ☐No ☐Unknown
3. Amnesia	☐Yes ☐No ☐Unknown
4. Altered behaviour or personality	☐Yes ☐No ☐Unknown
5. Depression	☐Yes ☐No ☐Unknown
6. Mood/behavioural concerns	☐Yes ☐No ☐Unknown
If yes, please describe:	
7. Headache	☐Mild ☐Moderate ☐Severe ☐No ☐Unknown
8. Periorbital pain	☐Yes ☐No ☐Unknown
9. Photophobia	☐Yes ☐No ☐Unknown
10. Neck stiffness	☐Yes ☐No ☐Unknown
11. Seizures	☐General ☐Focal ☐No ☐Unknown
12. Paralysis	☐General ☐Ascending ☐No ☐Unknown
If yes, please describe affected body parts and if progressive:	
13. Weakness	☐General ☐Focal ☐No ☐Unknown ○Power test (ie.confirmed by physical exam) ○Patient complaint
If focal, please describe affected body parts and if progressive:	
14. Numbness/tingling in extremities	☐Yes ☐No ☐Unknown
15. Movement disorder	☐Yes ☐No ☐Unknown
16. Oromotor dysfunction	☐Yes ☐No ☐Unknown
17. Sore throat	☐Yes ☐No ☐Unknown
18. Cough	☐Yes ☐No ☐Unknown
19. Conjunctivitis	☐Yes ☐No ☐Unknown
If yes, specify if:	☐Purulent ☐Non-purulent
20. Mouth ulcers	☐Yes ☐No ☐Unknown
21. Shortness of breath	☐Yes ☐No ☐Unknown
22. Chest pain	☐Yes ☐No ☐Unknown
23. Diarrhoea	☐Yes ☐No ☐Unknown
24. Vomiting/nausea	☐Yes ☐No ☐Unknown
25. Stomach pain	☐Yes ☐No ☐Unknown
26. Back pain	☐Yes ☐No ☐Unknown
27. Myalgia	☐Yes ☐No ☐Unknown
28. Arthralgia	☐Yes ☐No ☐Unknown
29. Joint swelling	☐Yes ☐No ☐Unknown
If yes, specify all affected joints:	○Fingers ○Toes ○Knee ○Elbow ○Other ☐ yes ☐ no if yes specify:_____

ZIKA VIRUS FOLLOW-UP CASE REPORT FORM: RAPID FORM

Participant's identification code: _____

30. Rash	☐Yes ☐No ☐Unknown	
If yes, please check box for type of rash and specify location:		**Spread of the rash:**
31. Maculopapular rash	☐Yes ☐No	☐Centrifugal ☐Centripetal
32. Erythematous rash	☐Yes ☐No	☐Centrifugal ☐Centripetal
33. Non blanching rash	☐Yes ☐No	☐Centrifugal ☐Centripetal
34. Vesicular rash	☐Yes ☐No	☐Centrifugal ☐Centripetal
35. Pruritic rash	☐Yes ☐No	☐Centrifugal ☐Centripetal
36. Petechial or purpuric rash	☐Yes ☐No	☐Centrifugal ☐Centripetal
37. Bruising/ ecchymosis	☐Yes ☐No	☐Centrifugal ☐Centripetal
38. If other type of rash, please specify:	Type: O face O torso O upper limbs O lower limbs O palms O other:	
39. Sign of insect bites	☐Yes ☐No ☐Unknown	
40. Jaundice	☐Yes ☐No ☐Unknown	
41. Bleeding	☐Yes ☐No ☐Unknown	
If yes, please state source (e.g. urine, stool):		

FOLLOW-UP OBSERVATIONS

42. Maximum Temperature	___°C ☐Oral ☐Tympanic ☐Axillary ☐Anal ☐Skin	
43. Respiratory Rate	_____breaths/minute	
44. Heart Rate	_____ beats/minute	
45. Systolic Blood Pressure	_____mmHg	
46. Diastolic Blood Pressure	_____mmHg	
47. Peripheral O_2 Saturation (SpO_2)	_____ % ☐Not recorded	
48. Glasgow Coma Score (out of 15)	___ / 15 OR ☐NA	
49. AVPU	☐A ☐V ☐P ☐U OR ☐NA	
50. Lymphadenopathy	☐Cervical only ☐General ☐No ☐Unknown	
51. Cardiovascular system	☐Normal ☐Abnormal ☐ Unknown	If abnormal, specify: ☐Murmur ☐Other:
52. Respiratory system	☐Normal ☐Abnormal ☐Unknown	If abnormal, describe:
53. Gastrointestinal system	☐Normal ☐Abnormal ☐Unknown	☐ Jaundice ☐ Abdominal tenderness ☐ Hepatomegaly ☐ Splenomegaly ☐ Hernia ☐ Omphaloceles ☐ Gastroschesis ☐Other (specify): _____
54. Neurological system	☐Normal ☐Abnormal ☐Unknown	☐ Paralysis – general ☐ Paralysis – ascending ☐ Paralysis – descending ☐ Hypotonia ☐ Weakness ☐ Stiffness or spasticity ☐ Abnormal movements (describe):_____ ☐Other (specify):

ZIKA VIRUS FOLLOW-UP CASE REPORT FORM: RAPID FORM

Participant's identification code: _____

		_____
55. Rash	☐Yes ☐No ☐Unknown	If yes, describe type of rash, body distribution: If yes, date of rash onset **(**DD/MM/YYY**):** **____/_____/20_____**
56. Dysmorphisms	☐Yes ☐No ☐Unknown	☐ Eye abnormalities ☐ Ear abnormalities ☐ Limb abnormalities ☐Other (specify):

NEW MEDICATIONS ADMINISTERED (since completion of previous form)

If no new medications administered, please tick here ☐ and proceed to section on laboratory results.

List all medications administered for acute symptoms: **Use generic names**, list all treatment given to the mother for this illness episode from date of onset.				
Type of medication	**Name of medication** (generic name)	**Start date** (dd/mm/yyyy)	**Number of days duration**	**Route of administration**
57. Antibiotics ☐Yes ☐No				☐IV ☐Oral
				☐IV ☐Oral
58. Antivirals ☐Yes ☐No				☐IV ☐Oral
				☐IV ☐Oral
59. Corticosteroids ☐Yes ☐No				☐IV ☐Oral ☐Topical ☐Inhaled
60. Anticonvulsants ☐Yes ☐No				☐IV ☐Oral
61. Anti-inflammatory (e.g. NSAIDs) ☐Yes ☐No				☐IV ☐Oral
62. Immunoglobulins ☐Yes ☐No				☐IV ☐Oral
63. Other (specify):				☐IV ☐Oral
Other (specify):				☐IV ☐Oral
Other (specify):				☐IV ☐Oral
Other (specify):				☐IV ☐Oral

LABORATORY RESULTS

Record all values available ≤24 hours of presentation/admission as part of the clinical care of patient included in the study. Please use standard (SI) units if possible. Please specify the unit used for each result. For repeat testing, use the most abnormal value per day copy page and ensure date of testing and patient IDs are indicated on each page.

If no laboratory results are available please tick here: ☐ and proceed to section on microbiological tests

Date of sampling (DD/MM/YYYY):	**__ / __ / 20 __**	

ZIKA VIRUS FOLLOW-UP CASE REPORT FORM: RAPID FORM

Participant's identification code: _____

Test		Value	Specify unit, if other specify unit used.
Inflammatory markers			
64. C-reactive protein	☐Yes ☐Not done ☐Unknown		☐mg/L ☐other:_____
65. Erythrocyte sedimentation rate	☐Yes ☐Not done ☐Unknown		☐mm/hr ☐other:_____
66. Procalcitonin	☐Yes ☐Not done ☐Unknown		☐ng/mL ☐other:_____
Haematology			
67. Haemoglobin	☐Yes ☐Not done ☐Unknown		☐g/L ☐g/dL ☐other:_____
68. Haematocrit	☐Yes ☐Not done ☐Unknown		☐% ☐other:_____
69. RBC count	☐Yes ☐Not done ☐Unknown		☐x10^9/L *or* ☐x10^3/µL ☐other:_____
70. MCV	☐Yes ☐Not done ☐Unknown		☐µm^3 ☐other:_____
71. White blood cell count	☐Yes ☐Not done ☐Unknown		☐x10^9/L ☐x10^3/µL ☐other:_____
72. Neutrophils	☐Yes ☐Not done ☐Unknown		☐**10^3/mm^3** ☐**%** ☐other:_____
73. Lymphocytes	☐Yes ☐Not done ☐Unknown		☐**10^3/mm^3** ☐**%** ☐other:_____
74. Monocytes	☐Yes ☐Not done ☐Unknown		☐**10^3/mm^3** ☐**%** ☐other:_____
75. Eosinophils	☐Yes ☐Not done ☐Unknown		☐**10^3/mm^3** ☐**%** ☐other:_____
76. Basophils	☐Yes ☐Not done ☐Unknown		☐**10^3/mm^3** ☐**%** ☐other:_____
77. Platelets	☐Yes ☐Not done ☐Unknown		☐x10^9/L *or* ☐x10^3/µL ☐other:_____
78. APTT	☐Yes ☐Not done ☐Unknown		☐seconds
79. PT (seconds)	☐Yes ☐Not done ☐Unknown		☐seconds
80. Blood film	☐Yes ☐Not done ☐Unknown		Describe results:
Biochemistry			
81. Urea nitrogen	☐Yes ☐Not done ☐Unknown		☐mmol/L ☐mg/dL ☐other:_____
82. Creatinine	☐Yes ☐Not done ☐Unknown		☐µmol/L ☐mg/dL ☐other:_____
83. Sodium	☐Yes ☐Not done ☐Unknown		☐mmol/L ☐other:_____
84. Potassium	☐Yes ☐Not done ☐Unknown		☐ mmol/L ☐other:_____
85. Total protein	☐Yes ☐Not done ☐Unknown		☐g/dL ☐other:_____
86. Albumin	☐Yes ☐Not done ☐Unknown		☐g/L ☐other:_____
87. Bilirubin	☐Yes ☐Not done ☐Unknown		☐µmol/L ☐mg/dL ☐other:_____
88. AST/SGOT	☐Yes ☐Not done ☐Unknown		☐U/L ☐other:_____
89. ALT/SGPT	☐Yes ☐Not done ☐Unknown		☐U/L ☐other:_____
90. GGT	☐Yes ☐Not done ☐Unknown		☐U/L ☐other:_____
91. ALP	☐Yes ☐Not done ☐Unknown		☐U/L ☐other:_____
92. Calcium	☐Yes ☐Not done ☐Unknown		☐mmol/L ☐other:_____
93. Phosphate	☐Yes ☐Not done ☐Unknown		☐mg/dL ☐other:_____
94. Magnesium	☐Yes ☐Not done ☐Unknown		☐mmol/L ☐other:_____
95. Amylase	☐Yes ☐Not done ☐Unknown		☐U/L ☐other:_____
96. Glucose	☐Yes ☐Not done ☐Unknown		☐mmol/L ☐mg/dL ☐other:_____
97. Creatine kinase	☐Yes ☐Not done ☐Unknown		☐U/L ☐other:_____
98. Other biochemistry result (specify):	☐Yes ☐Not done ☐Unknown		☐Unit:_____

ZIKA VIRUS FOLLOW-UP CASE REPORT FORM: RAPID FORM

Participant's identification code: _____

Other biochemistry result (specify):	☐Yes ☐Not done ☐Unknown		☐Unit:_____
If yes , describe results:			
99. Lumbar puncture	☐Yes ☐Not done ☐Unknown		

MICROBIOLOGICAL TESTS Record final diagnostics outcomes based on laboratory results, clinical picture and case definitions. Choose the appropriate case definition, e.g WHO or national/local case definition and ensure the definition used is clear and shared with all involved in the study.

If no microbiological results are available please tick here: ☐ and proceed to section on imaging

Pathogen	**Diagnosis**	**Date of onset** (DD/MM/YYYY)	**Comment**
100. Zika virus	☐ Confirmed acute infection ☐Probable acute infection ☐Confirmed past infection ☐Probable past infection ☐Negative ☐Not tested ☐Unknown	__ / ____ / 20 ___	
101. Dengue virus	☐ Confirmed acute infection ☐Probable acute infection ☐Confirmed past infection ☐Probable past infection ☐Negative ☐Not tested ☐Unknown	__ / ____ / 20 ___	
102. Yellow fever virus	☐ Confirmed acute infection ☐Probable acute infection ☐Confirmed past infection ☐Probable past infection ☐Negative ☐Not tested ☐Unknown	__ / ____ / 20 ___	
103. West Nile virus	☐ Confirmed acute infection ☐Probable acute infection ☐Confirmed past infection ☐Probable past infection ☐Negative ☐Not tested ☐Unknown	__ / ____ / 20 ___	
104. Chikungunya virus	☐ Confirmed acute infection ☐Probable acute infection ☐Confirmed past infection ☐Probable past infection		

ZIKA VIRUS FOLLOW-UP CASE REPORT FORM: RAPID FORM

Participant's identification code: _____

	☐Negative ☐Not tested ☐Unknown	__ / ____ / 20 ___	
105. Toxoplasmosis	☐ Confirmed acute infection ☐Probable acute infection ☐Confirmed past infection ☐Probable past infection ☐Negative ☐Not tested ☐Unknown	__ / ____ / 20 ___	
106. Rubella	☐ Confirmed acute infection ☐Probable acute infection ☐Confirmed past infection ☐Probable past infection ☐Negative ☐Not tested ☐Unknown	__ / ____ / 20 ___	
107. Cytomegalovirus	☐ Confirmed acute infection ☐Probable acute infection ☐Confirmed past infection ☐Probable past infection ☐Negative ☐Not tested ☐Unknown	__ / ____ / 20 ___	
108. Herpes Simplex virus	☐ Confirmed acute infection ☐Probable acute infection ☐Confirmed past infection ☐Probable past infection ☐Negative ☐Not tested ☐Unknown	__ / ____ / 20 ___	
109. Syphilis	☐ Confirmed acute infection ☐Probable acute infection ☐Confirmed past infection ☐Probable past infection ☐Negative ☐Not tested ☐Unknown	__ / ____ / 20 ___	
110. Other (specify):	☐ Confirmed acute infection ☐Probable acute infection ☐Confirmed past infection ☐Probable past infection ☐Negative	__ / ____ / 20 ___	
Other (specify):	☐ Confirmed acute infection ☐Probable acute infection ☐Confirmed past infection ☐Probable past infection ☐Negative	__ / ____ / 20 ___	

IMAGING

If no microbiological results are available please tick here: ☐ and proceed to section on outcome

ZIKA VIRUS FOLLOW-UP CASE REPORT FORM: RAPID FORM

Participant's identification code: _____

111. Imaging	**Results**	**If abnormal, please summarise key results:**	**Images attached**	**Report attached**
112. Cranial ultrasound scan	☐Normal ☐Abnormal ☐Not Done		☐Yes ☐No	☐Yes ☐No
113. MRI brain (record only if done as part of routine care)	☐Normal ☐Abnormal		☐Yes ☐No	☐Yes ☐No
114. CT brain (record only if part of routine care)	☐Normal ☐Abnormal		☐Yes ☐No	☐Yes ☐No
115. Other (specify type of test):	☐Normal ☐Abnormal		☐Yes ☐No	☐Yes ☐No
Other (specify type of test):	☐Normal ☐Abnormal		☐Yes ☐No	☐Yes ☐No

OUTCOME

116. Was the patient discharged home?	☐Yes ☐No ☐Unknown
117. Was the patient transferred to another facility/hospital?	☐Yes ☐No ☐Unknown If yes: ☐ICU ☐Ward ☐Emergency Department
118. If yes, please state name of the facility and city (address if possible):	
119. Please state reason for transfer:	
120. Did the patient die?	☐Yes ☐No ☐Unknown
If yes, please attach autopsy result if available:	

ZIKA VIRUS FOLLOW-UP CASE REPORT FORM: RAPID FORM

Participant's identification code: _____

CASE REPORT FORM COMPLETED BY

Name and role			
Signature		**Date** (DD/MM/YYY)	

Appendix D: Population Specific Zika Virus CRFs (not submitted to Scientific Review- Reviewed by external scientific panel)

Table A: list of all the more advanced case report forms (CRFs) that are available at the following link: https://zikainfection.tghn.org/research-tools-and-resources/crfs/

Document	Name	On ISARIC Website	Version submitted
Maternal CRFs	Baseline and Outcome	All on website	v6.1 05DEC2016
	Laboratory Results		v6.1 05DEC2016
	Intensive Care		v6.1 05DEC2016
	Acute Symptoms		v6.1 05DEC2016
	Antenatal Care		v6.1 05DEC2016
Neonates CRFs	Baseline and Outcome	All on website	v6.1 05DEC2016
	Laboratory Results		v6.1 05DEC2016
	Intensive care		v6.1 05DEC2016
Demographics and Epidemiology	To be used in combination with any of the above CRFs	On website	v4.1 07DEC2016
Child 0-5 years old	Baseline and Outcome	All on website	v2.0 07DEC2016
	Laboratory Results		v2.0 07DEC2016
	Intensive Care		v2.0 07DEC2016
	Acute Symptoms		v2.0 07DEC2016
	Follow up		v2.0 07DEC2016
Adult and Child >5	Baseline and Outcome	To be uploaded	v2.1 07DEC2016
	Laboratory Results		v2.1 07DEC2016
	Intensive Care		v2.1 07DEC2016
	Acute Symptoms		v2.1 07DEC2016
	Hospital stay		v2.1 07DEC2016

Returning Travellers	Baseline and Outcome	No	v3.0 15NOV2016
	Inpatient		V3.0.15NOV2016

Table B: Summary of case report forms available for specific populations

	Maternal	Neonatal	Child 0-5 Years	Adult and Child>5 Years	Returning Traveller
Acute symptoms	@		@	@	@
Baseline and outcome	@	@	@	@	@
Laboratory Results	@	@	@	@	@
Follow-up			@		
Hospital Stay				@	
Intensive Care		@	@	@	@

@ = there is a CRF available online at https://zikainfection.tghn.org/research-tools-and-resources/crfs/.

[INSTITUTIONAL LOGO]

Consent Form for Zika Virus Infection Natural History Protocol Study

(ADAPTED from ISARIC/WHO Clinical Characterisation Protocol for Severe Emerging Infections Study)

[*Study Title***]**	
[***Hospital name***]	**Patient name:**
Local lead investigator: [***local lead***]	**Patient number for this trial:**

INFORMATION SHEET FOR PATIENT

6 December 2016. Version 2.2

We are doing a research study involving people with possible Zika virus infection which is why we are inviting you to take part in this study.

Before you decide to participate, it is important for you to understand why the research is being done and what it involves. Please read this information carefully. Someone from our team is also available to go through the information with you and answer any questions. Please ask if there is anything that is not clear or if you would like more information and/or time to decide. Your participation is completely voluntary. Your decision will not affect your care or treatment in any way.

What is the study about?

Infectious diseases affect millions of people around the world every year. Most cases are mild, but some people become very sick. There is a lot that we do not understand about existing infections, and new infections continue to appear. This research study will gain important information about Zika virus so we can try to find better ways to take care of patients affected by these viruses in the future.

What will happen if I take part in this study?

We will collect information and possibly laboratory samples from you, which may be more than what would normally be collected for your medical care.

A blood sample may be taken now, together with [*** insert description of samples to be taken, for example: a swab from your nose and/or throat, , a saliva sample and a, urine sample (aka biologic samples)***]. If samples are required, you will be told in advance which samples are needed and how often samples will be taken. If other types of samples are required, this will be discussed with you in advance. We will try to take samples as part of routine care to minimize discomfort whenever possible.

[*** Insert description of when samples will be taken and amounts, for example: we may take similar samples again every second day over the next two weeks and then every week for as long as you are unwell (up to a maximum of 100 days). We will also invite you to return to the hospital or clinic in 3 and 6
months to have a blood sample taken. Each sample will take less than 15 mls (3 teaspoons) of blood***]. Any unused samples taken from you for regular care may be stored for future testing.

[***if protocol requires follow up, insert for example: when you have recovered we will also ask you to return to the hospital or clinic in 3 months and 6 months to have a blood sample taken***].

What will happen to the samples and information?

If samples are taken we will use them to learn more about the infection, look at how the body fights the infection, and how the treatments work. [*** insert only if DNA testing is part of protocol, for example: we may also use the blood sample to look at your genes (DNA) if you consent to this. We will examine your DNA together with DNA from many other people to try to find out what makes some people more susceptible to infection and to find information for development of new drugs against the infection***]. Some of your samples may be sent to other countries for testing, if you consent to this.

All of your information will be kept CONFIDENTIAL and only the people responsible for your care and for this study will know that you were a part of this study. We will review your medical records and keep limited information about you in a separate, secure file.

We would also like to store your samples and use them for future ethically approved medical research. The data and samples collected during this study may be used by public health agencies. The samples will only be labelled with a numbers, and results from any future research cannot be linked back to you.

Are there any benefits to taking part in this study?
There might not be any benefit to you personally. The information gained from this study may not be available in time or relevant to affect your care. Any results available while you are in hospital will be given to your treating doctor. The information we learn may help by improving diagnostics, care and treatment for people in the future.

What are the risks of taking part in the study?
Participating in this study means that if research samples are taken, then more samples will be taken than are needed for normal care. Whenever possible these samples will be taken at the same time as regular samples to reduce the extra procedures. There is a risk of pain or some discomfort when samples are taken.

[*** Insert if DNA testing is part of protocol, for example: if any sample will be used for DNA analysis, these results cannot be linked back to you and you will not be informed of any of these results***].

Can I request that I be withdrawn from the study at any point?
Yes, you can withdraw at any time without giving a reason and without affecting your care. Any samples that have not already been analysed can be destroyed anytime you request it.

Who is responsible and what if something goes wrong?
[***insert study Sponsor and contact details***]

What if I have any problems or would like further information about the study?
[***insert site Principal Investigator details***]

[INSTITUTIONAL LOGO]

Consent Form for Zika Virus Infection Natural History Protocol Study

(ADAPTED from ISARIC/WHO Clinical Characterisation Protocol for Severe Emerging Infections Study)

[*Study Title***]**	
[***Hospital name***]	**Patient name:**
Local lead investigator: [***local lead***]	**Patient number for this trial:**

INFORMED CONSENT FORM FOR PATIENT

2 December 2016. Version 2.2

Please initial box as appropriate

- ☐ I have read (or it has been read to me) the information sheet for this study. I understand the information and have had the opportunity to ask questions for clarification.
- ☐ I understand that my participation is voluntary and that I am free to withdraw from the study at any time, without giving any reason and without my medical care or rights being affected.
- ☐ I understand that data will be collected from my medical records by study staff and that this information may be looked at by [***insert the research organisations***] and authorised individuals from public health agencies. I agree that these individuals may have access to my research records.
- ☐ I understand that my information can be collected, analysed, reported and shared with others within and outside the country as part of this study. I understand that my name will not be used and I will not be identified

---

- ☐ I agree to collection of my clinical data
  OR IF YOU **DO NOT** AGREE, CHECK HERE ❑
- ☐ I agree to allow the use of my samples, taken for clinical purposes, to be used for research
  OR IF YOU **DO NOT** AGREE, CHECK HERE ❑
- ☐ I agree to provide biologic samples as described in this leaflet on the day of enrolment
  OR IF YOU **DO NOT** AGREE, CHECK HERE ❑
- ☐ I agree to provide serial biologic samples as described in this leaflet for the study
  OR IF YOU **DO NOT** AGREE, CHECK HERE ❑
- ☐ I agree that my samples may be sent elsewhere in the world to be analysed.
  OR IF YOU **DO NOT** AGREE, CHECK HERE ❑
- ☐ [*** Insert this clause only if DNA testing is required by protocol: I agree that DNA from my blood sample will be analysed to determine whether any genetic factors have made me susceptible to infection and severe of infection experienced.
  OR IF YOU **DO NOT** AGREE, CHECK HERE ❑***]
- ☐ I agree that my blood sample, [*** insert if appropriate 'including my DNA'***], may be used in additional research in the future, if necessary in different parts of the world, as long as appropriate ethical approval is in place.
  OR IF YOU **DO NOT** AGREE, CHECK HERE ❑

- ☐ I agree to be contacted directly by the investigators with an invitation to participate in future research studies.
  OR IF YOU **DO NOT** AGREE, CHECK HERE ❑
- ☐ I agree to the collection and analysis of autopsy/post-mortem samples and/or tissues if this situation were to arise.
  OR IF YOU **DO NOT** AGREE, CHECK HERE ❑

Patient Name:_____ Signature/fingerprint:_____
Date:_____

Person taking consent:_____ Signature:_____
Date:_____

Witnessed Consent

If the consenting party cannot read the form: I have no interest or involvement in this research study and I attest that the information concerning this research was accurately read and explained to the patient in a language they can understand, and that informed consent was freely given by the patient.

Witness name:_____ Signature/fingerprint:_____
Date:_____

[INSTITUTIONAL LOGO]

Consent Form for Zika Virus Infection Natural History Protocol Study

(ADAPTED from ISARIC/WHO Clinical Characterisation Protocol for Severe Emerging Infections Study)

[*Study Title***]**	
[***Hospital name***]	**Patient name:**
Local lead investigator: [***local lead***]	**Patient number for this trial:**

INFORMATION SHEET FOR CONSULTEE

6 December 2016. Version 2.2

We are doing a research study involving people with possible Zika virus infection which is why we are inviting _____patient's name) (from hereon referred to as the "participant") to take part in this study.

Before you decide it is important for you to understand why the research is being done and what it involves. Please take time to read this information carefully. Someone from our team is also available to go through the information with you and answer any questions. Please ask if there is anything that is not clear or if you would like more information and/or time to decide. The participant's involvement is completely voluntary. Your decision will not affect his/her care or treatment in any way.

What is the study about?

Infectious diseases affect millions of people around the world every year. Most cases are mild, but some people become very sick. There is a lot that we do not understand about existing infections, and new infections continue to appear. This research study will gain important information about Zika virus infection so we can try to find better ways to take care of patients affected by these viruses in the future.

What will happen if the participant takes part in this study?

We will collect information and possibly samples which may be more than what would normally be collected for the participant's medical care.

A blood sample may be taken now, together with [***insert description of samples to be taken, for example - a swab from the nose and/or throat, , a saliva sample, and a urine sample (aka biologic samples)-***]. If samples are required, you will be told in advance which samples are needed and how often samples will be taken. If other types of samples are required, this will be discussed in advance. We will try to take samples as part of routine care to minimize discomfort whenever possible.

[***insert a short description of the samples that are to be taken, when and the amount, for example: we may take similar samples again every second day over the next two weeks and then every week for as long as the participant is unwell. We will also invite the participant to return to the hospital or clinic in 3 and 6 months to have a blood sample taken. Each sample will take less than 15 mls (3 teaspoons) of blood***]. Any leftovers from samples taken for regular care may be stored for future testing.

[***if protocol requires follow up, insert for example: when the participant has recovered we will also ask the participant to return to the hospital or clinic in 3 months and 6 months to have a blood sample taken***].

What will happen to the samples and information?
If samples are obtained we will use them to learn more about the infection, look at how the body fights the infection, and how the treatments work. [*** insert only if DNA testing is part of protocol, for example: we may also use the blood sample to look at the participant's genes (DNA) if you consent to this. We will examine this DNA together with DNA from many other people to try to find out what makes some people more susceptible to infection and to find information for development of new drugs against the infection ***]. Some of the samples may be sent to other countries for testing if you consent to this.

All of the participant's information will be kept CONFIDENTIAL and only the people responsible for their care and for this study will know that they were a part of this study. We will review their medical records and keep limited information in a separate secure file. [*** Take this sentence out for studies providing real time diagnostics -All information and samples will be labelled with a number only, so that they cannot be directly linked to you***].

We would also like to store their samples and use them for future ethically approved medical research. The data and samples collected during this study may be used by public health agencies. The samples will only be labelled with a numbers, and results from any future research cannot be linked back to you.

Are there any benefits to taking part in this study?
There might not be any benefit to the participant. The information gained from this study may not be available in time or relevant to affect their care. Any results available while they are in hospital will be given to their treating doctor. The information we learn may help by improving diagnostics, care and treatment for people in the future.

What are the risks of taking part in the study?
Participating in this study means that if research samples are taken, then more samples will be taken than are needed for normal care. Whenever possible these samples will be taken at the same time as regular samples to reduce the extra procedures. There is a risk of pain or some discomfort when samples are taken.

[*** Insert if DNA testing is part of protocol, for example: if any sample will be used for DNA analysis, these results cannot be linked back to you and you will not be informed of any of these results].

What are the legal implications if I consent on the patient's behalf now and s/he does not agree when s/he recovers?
As the consultee it is your role to make the best decision based on your knowledge of the participant's wishes. If the participant does not agree when s/he recovers they may withdraw from the study at any time without giving a reason and without affecting their care. Any samples that have not already been analysed can be destroyed anytime they request it.

Can the participant be withdrawn from the study at any point?
Yes, the participant can withdraw at any time without giving a reason and without affecting their care. Any samples that have not already been analysed can be destroyed anytime they request it.

Who is responsible and what if something goes wrong?
[***insert study Sponsor and contact details***]

What if the participant or I have any problems or would like further information about the study?
[***insert site Principal Investigator details***]

[INSTITUTIONAL LOGO]

Consent Form for Zika Virus Infection Natural History Protocol Study

(ADAPTED from ISARIC/WHO Clinical Characterisation Protocol for Severe Emerging Infections Study)

[*Study Title***]**	
[***Hospital name***]	**Patient name:**
Local lead investigator: [***local lead***]	**Patient number for this trial:**

DECLARATION OF UNDERSTANDING FOR CONSULTEE
6 December 2016. Version 2.2

Please initial box as appropriate

- ☐ I have been consulted about [ ]'s participation in this research project. I have read (or it has been read to me) the information sheet for this study. I understand the information and have had the opportunity to ask questions for clarification.
- ☐ I understand that the participant's participation is voluntary and that the participant is free to withdraw from the study at any time, without giving any reason and without their medical care or rights being affected.
- ☐ I understand that data will be collected from the participant's medical records by study staff and that this information may be looked at [***insert the research organisation***] by authorised individuals from public health agencies. I agree that these individuals may have access to the participant's research rec- ords.
- ☐ I understand that the participant's information and samples can be collected, analysed, reported and shared with others outside the country. I understand that participant's name will not be used and they will not be identified.

- ☐ I agree to collection of the participant's clinical data
  OR IF YOU **DO NOT** AGREE, CHECK HERE ❑
- ☐ I agree to allow the use of the participant's samples, taken for clinical purposes, to be used for research
  OR IF YOU **DO NOT** AGREE, CHECK HERE ❑
- ☐ I agree to the collection of biologic samples from the participant as described in the leaflet on the day of enrolment
  OR IF YOU **DO NOT** AGREE, CHECK HERE ❑
- ☐ I agree to the collection of serial biologic samples from the participant as described in the leaflet for the study
  OR IF YOU **DO NOT** AGREE, CHECK HERE ❑
- ☐ I agree that the participant's samples may be sent elsewhere in the world to be analysed.
  OR IF YOU **DO NOT** AGREE, CHECK HERE ❑
- ☐ [*** Insert this clause only if DNA testing is required by protocol: I understand that DNA from the participant's blood sample will be analysed to determine whether any genetic factors have made him/her susceptible to infection and severe of infection experienced.

OR IF YOU **DO NOT** AGREE, CHECK HERE ❑***]

- ☐ I understand that the participant's blood sample, [*** insert if appropriate 'including my DNA'***], may be used in additional research in the future, if necessary in different parts of the world, as long as appropriate ethical approval is in place.
  OR IF YOU **DO NOT** AGREE, CHECK HERE ❑
- ☐ I understand that the participant may be contacted directly by the investigators with an invitation to participate in future research studies.
  OR IF YOU **DO NOT** AGREE, CHECK HERE ❑
- ☐ I understand that the participant's autopsy/post-mortem samples and/or tissues if this situation were to arise.
  OR IF YOU **DO NOT** AGREE, CHECK HERE ❑

Consultee's name:_____Signature/fingerprint:_____
Date:_____

Person taking consent: _____Signature:_____
Date:_____

Witnessed Consent

If the consenting party cannot read the form: I have no interest or involvement in this research study and I attest that the information concerning this research was accurately read and explained to the patient in language they can understand, and that informed consent was freely given by the patient.

Witness name:_____Signature/fingerprint:_____
Date:_____

[INSTITUTIONAL LOGO]

Consent Form for Zika Virus Infection Natural History Protocol Study

(ADAPTED from ISARIC/WHO Clinical Characterisation Protocol for Severe Emerging Infections Study)

[*Study Title***]**	
[***Hospital name***]	**Patient name:**
Local lead investigator: [***local lead***]	**Patient number for this trial:**

INFORMATION SHEET FOR PARENT / GUARDIAN

6 December 2016. Version 2.2

We are doing a research study involving people with possible Zika virus infection, which is why we are inviting your child, _____(child's name) (from hereon referred to as the "participant") to take part in this study.

Before you decide it is important for you to understand why the research is being done and what it involves. Please take time to read this information carefully. Someone from our team is also available to go through the information with you and answer any questions. Please ask if there is anything that is not clear or if you would like more information and/or time to decide. The participant's involvement is completely voluntary. Your decision will not affect their care or treatment in any way.

What is the study about?

Infectious diseases affect millions of people around the world every year. Most cases are mild, but some people become very sick There is a lot that we do not understand about existing infections, and new infections continue to appear. This research study will gain important information about [*** insert as appropriate 'name of infection(s)' or 'Zika virus infection' ***] so we can try to find better ways to take care of patients affected by these viruses in the future.

What will happen if the participant takes part in this study?

We will collect information and possibly samples which may be more than what would normally be collected for the participant's medical care.

A blood sample may be taken now, together with [***insert description of samples to be taken, for example - a swab from the nose and/or throat, a saliva sample and a, urine sample (aka biologic samples)]. If samples are required, you will be told in advance which samples are needed and how often samples will be taken. If other types of samples are required, this will be discussed in advance. We will try to take samples as part of routine care to minimize discomfort whenever possible.

[***insert a short description of the samples that are to be taken, when and the amount, for example: we

may take similar samples again every second day over the next two weeks and then every week for as long as the participant is unwell. We will also invite the participant to return to the hospital or clinic in 3 and 6 months to have a blood sample taken. Each sample will take less than 15 mls (3 teaspoons) of blood***].

Any leftovers from samples taken for regular care may be stored for future testing.

.

[***if protocol requires follow up, insert for example: when the patient has recovered we will also ask you to return with him/her to the hospital or clinic in 3 months and 6 months to have a blood sample taken***].

What will happen to the samples and information?

If samples are obtained we will use them to learn more about the infection, look at how the body fights the infection, and how the treatments work. [*** insert only if DNA testing is part of protocol, for example: we may also use the blood sample to look at the participant's genes (DNA) if you consent to this. We will examine this DNA together with DNA from many other people to try to find out what makes some people more susceptible to infection and to find information for development of new drugs against the infection ***]. Some of the samples may be sent to other countries for testing, if you consent to this.

All of the participant's information will be kept CONFIDENTIAL and only the people responsible for their care and for this study will know that they were a part of this study. We will review their medical records and keep limited information in a separate secure file. [*** Take this sentence out for studies providing real time diagnostics -All information and samples will be labelled with a number only, so that they cannot be directly linked to you***].

We would also like to store their samples and use them for future ethically approved medical research. The data and samples collected during this study may be used by public health agencies. The samples will only be labelled with a numbers, and results from any future research cannot be linked back to you.

Are there any benefits to taking part in this study?

There might not be any benefit to the participant. The information gained from this study may not be available in time or relevant to affect their care. Any results available while they are in hospital will be given to their treating doctor. The information we learn may help in caring for other patients in the future.

What are the risks of taking part in the study?

Participating in this study means that if research samples are taken, then more samples will be taken than are needed for normal care. Whenever possible these samples will be taken at the same time as regular samples to reduce the extra procedures. There is a risk of pain or some discomfort when samples are taken.

[*** Insert if DNA testing is part of protocol, for example: if any sample will be used for DNA analysis, these results cannot be linked back to you and you will not be informed of any of these results***].

Can the participant be withdrawn from the study at any point?

Yes, the participant can withdraw at any time without giving a reason and without affecting their care. Any samples that have not already been analysed can be destroyed anytime they request it.

Who is responsible and what if something goes wrong?

[***insert study Sponsor and contact details***]

What if the participant or I have any problems or would like further information about the study?

[***insert site principal investigator details***]

[INSTITUTIONAL LOGO]

Consent Form for Zika Virus Infection Natural History Protocol Study

(ADAPTED from ISARIC/WHO Clinical Characterisation Protocol for Severe Emerging Infections Study)

[***Study Title***]	
[***Hospital name***]	**Patient name:**
Local lead investigator: [***local lead***]	**Patient number for this trial:**

PARENT/GUARDIAN CONSENT FORM

6 December 2016. Version 2.2

Please initial box as appropriate

- ☐ I have been consulted about my child, [ ]'s participation in this research project. I have read (or it has been read to me) the information sheet for this study. I understand the information and have had the opportunity to ask questions for clarification.
- ☐ I understand that his/her participation is voluntary and that I am free to withdraw him/her from the study at any time, without giving any reason and without his/her medical care or rights being affected.
- ☐ I understand that data will be collected from his/her medical records by study staff during the study and that this information may be looked at by [***insert the research organization***] and authorized individuals from public health agencies. I agree that these individuals may have access to his/her research records and study results.
- ☐ I understand that his/her information and samples can be collected, analysed, reported and shared with others outside the country elsewhere in the world. I understand that his/her name will not be used and will not be identified.
- ☐ I understand his/her samples may be sent elsewhere in the world to be analysed.

- ☐ I agree to collection of the participant's clinical data
  OR IF YOU **DO NOT** AGREE, CHECK HERE ❑
- ☐ I agree to allow the use of the participant's samples, taken for clinical purposes, to be used for research
  OR IF YOU **DO NOT** AGREE, CHECK HERE ❑
- ☐ I agree to the collection of biologic samples from the participant as describe in the leaflet on the day of enrolment
  OR IF YOU **DO NOT** AGREE, CHECK HERE ❑
- ☐ I agree to the collection of serial biologic samples from the participant as describe in the leaflet for the study
  OR IF YOU **DO NOT** AGREE, CHECK HERE ❑
- ☐ I agree that the participant's samples may be sent elsewhere in the world to be analysed.
  OR IF YOU **DO NOT** AGREE, CHECK HERE ❑

☐ [*** Insert this clause only if DNA testing is required by protocol: I understand that DNA from the participant's blood sample will be analysed to determine whether any genetic factors have made him/her susceptible to infection and severe of infection experience. OR IF YOU **DO NOT** AGREE, TICK/INITIAL HERE ❑***]

- ☐ I understand that the participant's blood sample, [*** insert if appropriate 'including my DNA'***], may be used in additional research in the future, if necessary in different parts of the world, as long as appropriate ethical approval is in place.
  OR IF YOU **DO NOT** AGREE, CHECK HERE ❑
- ☐ I understand that I might be contacted directly by the investigators with an invitation for him/her to participate in future research studies.
  OR IF YOU **DO NOT** AGREE, CHECK HERE ❑
- ☐ I understand that the participant's autopsy/post-mortem samples and/or tissues if this situation were to arise.
  OR IF YOU **DO NOT** AGREE, CHECK HERE ❑
- ☐

Parent/guardian's name:_____Signature/fingerprint:_____
Date:_____

Person taking consent:_____Signature:_____
Date:_____

Witnessed Consent

If the consenting party cannot read the form: I have no conflict of interest orinvolvement in this research study and I attest that the information concerning this research was accurately read and explained to the patient in language they can understand, and that informed consent was freely given by the patient.

Witness name:_____Signature/fingerprint:_____
Date:_____

[*** Insert only if appropriate in Country: ASSENT OF COMPETENT YOUNG PEOPLE
Consistent with best practice, and when appropriate, children and young people should be invited to indicate they are willing to participate in this study (assent). Should a competent young person decline to being involved, the young person's decision should be respected.
Where a child or young person is unable to express their wishes for reasons of acute illness (or otherwise), their views should be sought and recorded at the earliest opportunity once recovered.
Separate assent forms are available for young children (age <12 years) and young people (age 12 to 16/17 years)***]

[INSTITUTIONAL LOGO]

Consent Form for Zika Virus Infection Natural History Protocol Study

(ADAPTED from ISARIC/WHO Clinical Characterisation Protocol for Severe Emerging Infections Study)

[*Study Title***]**	
[***Hospital name***]	**Patient name:**
Local lead investigator: [***local lead***]	**Patient number for this trial:**

INFORMATION SHEET FOR YOUNG PERSON AGE 12 TO 17 YEARS OLD

6 December 2016. Version 2.2

We are doing a research study involving people with new infections such as Zika virus infection. We have come you to ask if you would be willing to help us because you may have this infection.

Before deciding if you want to be involved, it is important for you to understand why this research is being done and what it would involve for you. One of our team will go through the information with you. Please ask us if there is anything that is not clear, or if you would like more information

What is the study about?

- Infectious diseases affect millions of people around the world every year.
- New infections appear and sometimes there is a lot that we do not understand about these new infections.
- By understanding why young people like you are sick we can try to find better ways to manage and treat people in the future.

Do I have to take part?

- **The short answer is: No**
- You and your parents/guardians/career can decide if you want to be involved.
- If you don't want to be involved, then you don't have to.
- Either way, your decision will not affect your care and treatments in any way: the choice is up to you

What will happen if I take part in this study?

We will collect information from your clinical records when you are in hospital. We may collect samples that are extra to what would normally be collected for your normal care in hospital. If samples are taken, each time we will take:

- blood samples, a swab from your nose and/or throat, saliva, and urine
- [***insert list of samples to be taken using simple accessible language***]

The amount of blood will be small and will depend on your weight so that we only take a safe amount. The study staff can tell you how much blood will be taken at each visit.
Whenever possible these samples will be taken at the same time as regular samples to reduce the extra procedures.
[*** insert what samples will be taken and when***].
If there are unused extra samples taken for your regular care, we may store these leftovers for this research.

[***if protocol requires follow up, insert for example: when you have recovered we will also ask you to return to the hospital or clinic in 3 months and 6 months to have a blood sample taken***].

What will happen to my information?
All information about you will be CONFIDENTIAL. Only the people responsible for your care and for this study will know that you were involved in this study.
If you agree, we will also store your anonymous data and use it for future approved related medical research. The data collected during this study at any time may be seen and shared with public health agencies.

What will happen to my samples?
We will use your blood samples to look at how your body fights the infection and how the treatment given works in your body. [If DNA testing is required in protocol, insert for example: we will also examine your genes (DNA) together with the DNA from many other people to try to find out what makes some people more likely to get severe infection***]. Some of the tests may be done in different countries.

If you agree, we will also keep samples for possible future use in other related medical research. This will only be done as a properly approved study. The samples collected during this study may be seen and shared with public health agencies.

Are there any benefits to taking part in this study?
There might not be any benefits for you personally. By helping us find out more about why you are ill, we will be able to help look after young people better in the future.

What are the risks of being in the study?
If only clinical data is collected there is a minimum risk, all information will be used anonymously (no one will know your name). If samples are taken there is a small risk of pain or irritation when samples are taken. [*** Insert if DNA testing is part of protocol, for example: if any samples will be used for DNA analysis, these results cannot be linked back to you and you will not be informed of any of these results***].

[INSTITUTIONAL LOGO]

Consent Form for Zika Virus Infection Natural History Protocol Study

(ADAPTED from ISARIC/WHO Clinical Characterisation Protocol for Severe Emerging Infections Study)

[*Study Title***]**	
[***Hospital name***]	**Patient name:**
Local lead investigator: [***local lead***]	**Patient number for this trial:**

YOUNG PERSON ASSENT, AGE 12 TO /17 YEARS OLD

6 December 2016. Version 2.2

ASSENT OF COMPETENT YOUNG PEOPLE

Consistent with best practice, when appropriate children and young people should be invited to indicate they are willing to participate in this study (assent). Should a competent young person decline to being involved, the young person's decision should be respected.

Please tick ✓ the box if you agree.

1. I have read the leaflet about the study and understand it. ☐
2. I know I do not have to take part if I don't want to and can change my mind. The doctors and nurses will still look after me. ☐
3. I do not mind if someone doing the research looks at my medical records to see if the study is done in the right way. I know the people doing the research will keep personal things about me private. ☐
4. I agree to take part in the study and to share information from my medical records. ☐
5. I agree to take part in the study and to give samples for the study. ☐
6. I agree to let someone talk to me about another study in the future, after this study ends. OR IF YOU DO NOT AGREE, TICK HERE [ ] ☐

Name of Patient Date Signature

Name: _____ Relationship: _____
(Legal Guardian/Career Name in Block Letters)

Name of Person taking consent Date Signature
(Research team member or health professional trained in taking consent for this study)

Researcher Date Signature

[INSTITUTIONAL LOGO]

Consent Form for Zika Virus Infection Natural History Protocol Study

(**ADAPTED from ISARIC/WHO Clinical Characterisation Protocol for Severe Emerging Infections Study)**

[*Study Title***]**	
[***Hospital name***]	**Patient name:**
Local lead investigator: [***local lead***]	**Patient number for this trial:**

INFORMATION SHEET FOR CHILDREN YOUNGER THAN 12 YEARS OLD
6 December 2016. Version 2.1

Parents/guardians/careers are asked to go through this information with their child. Please consider using a cartoon sheet to explain the study to young children.
Please ask study staff if you or your child has any questions.

We want to find out most about the infection that has made you sick so that we can help other children like you.

What does this mean for me?
To help us finding out more about what is making you and other children sick we will collect information from your medical records when you are in hospital.

In addition we may take some extra samples of blood and other samples while you are in hospital.

These are extra to what would normally be collected for your care. Each time we will take:

- a small blood sample, saliva, urine
- [***insert a list of other samples describing them in child friendly terminology***]

The amount of blood will depend on how big you are. We will weight you so that we only take a safe amount. We will explain how much blood will be taken at each visit. We will also keep any extra samples from your normal care. We will make sure the amount of blood is as small as possible.

[***Insert when the samples will be taken, for example: we will take the same samples every other day for two weeks, and then every week for as long as you are unwell***]. When you are better [*** if protocol requires follow up, insert for example: we will ask you to come back to the hospital or clinic in 3 and 6 month time to give us one more blood sample***].

Do I have to take part?
No, it is your choice. Your parents can help you decide.
If you don't want to take part, then you don't have to. Your decision will not affect your care and treatments in any way.

What will happen to the information and samples?
All information about you will be kept private. Only the people responsible for your care and for this study will know that you were involved in this study.

If you agree for us to take samples, we will use the samples to see how your body fights the infection and how well medicines given to you work to make you better. All information about you will be kept private.

Are there any benefits to taking part in this study?

It may not be any benefit for you. By helping us find out more about why you are sick, we will be able to help look after children better in the future. In addition to the data we collect, if samples are taken, being a part of this study means that more samples will be taken than are needed for normal care.

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Consent Form for Zika Virus Infection Natural History Protocol Study

(**ADAPTED from ISARIC/WHO Clinical Characterisation Protocol for Severe Emerging Infections Study)**

[*Study Title***]**	
[***Hospital name***]	**Patient name:**
Local lead investigator: [***local lead***]	**Patient number for this trial:**

CHILDREN YOUNGER THAN 12 YEARS OLD – ASSENT FORM
6 December 2016. Version 2.2

Please tick ✓ the boxes if you agree. If you don't agree, leave the boxes empty.

I have been told about the study and given the information sheet about it and have had the chance to ask questions. ☐

I know I don't have to take part. If I do, I can change my mind – the doctors and nurses will still look after me. ☐

I do not mind if someone doing the research looks at my medical records and collects my information - I know the people doing the study will keep personal things about me private. ☐

I understand samples for the study may be collected from me when I am in hospital. ☐

I agree to take part. ☐

Name of Patient Date Signature

Name: _____ Relationship: _____
(Legal Guardian/Career Name in Block Letters)

Name of Person taking consent Date Signature
(Research team member or health professional trained in taking consent for this study)

Researcher Date Signature