Protocol Number: INA107

INA-RESPOND Observational Research on Infectious Disease Outbreaks and Difficult Cases of Unidentified Etiology in Indonesia

Sponsored by:

Centre for Research and Development of Health Resources and Services, National Institute of Health Research and Development (NIHRD), Ministry of Health, Indonesia

National Institute of Allergy and Infectious Diseases (NIAID), National Institutes of Health, United States

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Protocol Summary

Long title	INA-RESPOND **O**bservational **R**esear**ch** on **I**nfectious **D**isease outbreaks and difficult cases of unidentified etiology in Indonesia
Short title	INA-ORCHID
Study number	INA107
Clinical trial identifier	NCT04339179
Rationale	Infectious diseases remain a significant source of morbidity and mortality in Indonesia, and sudden disease outbreaks can rapidly spread throughout the country and beyond. Containing outbreaks that might lead to pandemics is a crucial public health operation that is strengthened by clinical research studies on the etiologies, epidemiology, clinical manifestations, and case management processes of infectious diseases. The INA-RESPOND Network maintains an extensive and experienced research presence across Indonesia that is capable of conducting research on ongoing infectious disease outbreaks and difficult cases of unidentified etiology. This protocol will leverage the unique capacity of the INA-RESPOND Network to rapidly study sudden disease outbreaks, difficult infectious disease cases of unidentified etiology, and samples collected during historical outbreaks and cases of unknown etiologies. The outcomes of this research will significantly improve our understanding of circulating diseases in Indonesia, particularly those that are most challenging to identify and of greatest outbreak concern.
Objectives	**Aim** To understand the scope of pathogens responsible for outbreaks and difficult clinical cases in Indonesia, and to characterize the clinical course of the diseases to better inform diagnostics, treatments, and prevention strategies. **Objective** **Primary objective:** To identify the causative agents and describe the clinical characteristics of presumptive infections reported during infectious diseases outbreaks or referred from difficult cases of unidentified etiology in Indonesia. **Secondary objectives:** • To describe the disease course and case management of the presumptive infections • To assess the accuracy of diagnostic tests of the presumptive infections • To assess treatments and short-term outcomes of the presumptive infections • To generate epidemiologic data to inform ongoing and future disease control and prevention efforts

Study design	This is a study to identify the causative agents and describe the clinical characteristics of infectious disease outbreaks and difficult cases of unidentified etiology in Indonesia. It is a retrospective and prospective observational study with an exploratory design. There will be no intervention to the participants that is intended to affect their standard of care or clinical outcome. Retrospective study activities will be ongoing throughout the duration of the study. The INA-RESPOND Reference Lab will perform research tests on various specimens collected as part of historical outbreaks and previous difficult cases where an etiology was never identified. Prospective study activities will be initiated upon official request from health authorities and health facilities/institutions. Requests are expected to be filtered through and evaluated by the **20** active INA-RESPOND Network sites before inclusion in the study. Samples collected during outbreaks and from difficult cases of unknown etiology will be analyzed at the INA-RESPOND Reference Lab at their own pace. Results from any research tests will be shared with the requesting authorities as research-use-only and are not intended to alter standard of care.
Sample size	This is a 5-year study that will enroll an estimated total of 2,000 prospective cases, with a ceiling of 4,000 cases if necessary. The study will also include an estimated total of 500 retrospective cases, with a ceiling of 1,000 cases if necessary.
Visit schedule for prospective study arm of ongoing patients providing informed consent	**Study Visit 1: Enrollment and Baseline Visit (Day 0)** 1. Demographics including, but not limited to: sex, age, residence, occupation. 2. Medical history including, but not limited to: travel history, insect and animal exposure, vaccination history, medication use prior to enrollment. 3. Clinical data including, but not limited to: current signs and symptoms, height and weight, vital signs, comorbidities, treatment, clinical outcome at this visit, available SoC laboratory or imaging results. 4. Specimen collection **(when possible)**: whole blood (5-15 mL) and clinically indicated non-invasive specimens such as sputum, urine, stool, nasopharyngeal swab, etc. Specimens collected under SoC can also be included in the study if leftover material is shared. 5. Laboratory testing: routine hematology, blood chemistry, liver function tests, and renal function tests. **Study Visit 2: Follow-Up Visit (between Day 7-14)** 1. Clinical data including, but not limited to: current signs and symptoms, height (if previously not done) and weight, vital signs, comorbidities, treatment, clinical outcome at this visit, available SoC laboratory or imaging results. 2. Specimen collection **(when possible)**: whole blood (5-15 mL) and clinically indicated non-invasive specimens such as sputum,

	urine, stool, nasopharyngeal swab, etc. Specimens collected under SoC can also be included in the study if leftover material is shared. 3. Clinical outcome data at hospital discharge or death (when applicable). **Study Visits After Visit 2, if Needed** 1. Clinical data including, but not limited to: current signs and symptoms, height (if previously not done) and weight, vital signs, comorbidities, treatment, clinical outcome at this visit, available SoC laboratory or imaging results. 2. Specimen collection **(when possible)**: whole blood (5-15 mL) and clinically indicated non-invasive specimens such as sputum, urine, stool, nasopharyngeal swab, etc. Specimens collected under SoC can also be included in the study if leftover material is shared. 3. Clinical outcome data at hospital discharge or death (when applicable). **Interim Visits as part of Standard of Care** At any time between study visits, clinical data and leftover specimen material collected as part of SoC visits could also be included in the study if shared by the attending clinician. These interim visits are independent of the study and may or may not occur depending on SoC procedures.

Table of Content

List of Figures and Table

List of Abbreviations and Acronyms

AE	Adverse Events
BAL	Bronchoalveolar Lavage
COVID-19	Coronavirus Disease
Co-PI	Co-Principal Investigator
CRF	Case Report Form
CSF	Cerebrospinal Fluid
DNA	Deoxyribonucleic Acid
EDMS	Electronic Document Management System
ICH-GCP	International Conference on Harmonization Guidelines for Good Clinical Practice
ICF	Informed Consent Form
ID	Identification
IEC	Institutional Ethics Committee
IgM	Immunoglobulin M
INA-RESPOND	Indonesia Research Partnership on Infectious Diseases
IRB	Institutional Review Board
LAR	Legally Accepted Representative
MERS	Middle East Respiratory Syndrome
MoH	Ministry of Health of Indonesia
MP	Monitoring Plan
MTA	Material Transfer Agreement
NIAID	National Institute of Allergy and Infectious Diseases
NIH	National Institutes of Health
NIH-HRPP	National Institutes of Health Human Research Protection Program
NIHRD	National Institute of Health Research and Development
NP	Nasopharyngeal
OHRP	Office for Human Research Protections
OP	Oropharyngeal
PBMC	Peripheral Blood Mononuclear Cell
PI	Principal Investigator
PII	Personal Identifiable Information
RE	Reportable Event
RT-PCR	Reverse Transcription Polymerase Chain Reaction
SAE	Serious Adverse Event
SARS	Severe Acute Respiratory Syndrome
UP	Unanticipated Problem
VTM	Virus Transport Media

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1. Introduction

Pandemics are large-scale outbreaks of infectious diseases that can significantly increase morbidity and mortality over a wide geographic area and cause significant economic, social, and political disruption. In the 21st century, the world has endured several prominent pandemics caused by severe acute respiratory syndrome (SARS) beta coronavirus, influenza A/H5N1, Middle East respiratory syndrome (MERS) beta coronavirus, influenza A/H1N1, Ebola virus, Zika virus, and currently the 2019 novel beta coronavirus (Covid-19). As pandemics generally begin from localized outbreaks, swiftly mitigating emerging outbreaks is crucial to global health. While a rapid public health investigation is essential to understand the epidemiology, clinical manifestations, and control of the suspected diseases, a scientific research response is necessary to systematically identify the best diagnostics, treatments, and prevention strategies.

The Indonesia Research Partnership on Infectious Diseases (INA-RESPOND) is a nation-wide research network with **20** active hospital sites and a sophisticated central research laboratory capable of screening and identifying a variety of pathogens. In response to outbreaks, INA-RESPOND can leverage its extensive network and scientific experience to conduct the research needed to mitigate outbreaks, improve case management, select effective and efficient diagnostic tests, and develop treatment and prevention strategies. In addition to housing the capacity to conduct research during outbreaks, INA-RESPOND can also conduct research on suspected infectious disease cases of unidentified etiology reported by clinicians at healthcare facilities. Since outbreak pathogens are often unpredictable, and since each outbreak begins with a patient zero, it is important to monitor and strengthen the Indonesian healthcare system at all levels to help prevent outbreaks before they even begin.

This observational study will investigate suspected infectious diseases of unknown etiology prospectively during outbreaks and at healthcare facilities, and retrospectively through historical samples where no etiology was ever determined. The study is designed to rapidly, flexibly, and consistently respond to any potential scenario in Indonesia, and the data collected will provide needed

insight into the landscape of infectious diseases in the country. By better understanding the infectious causes of outbreaks and difficult hospitalized cases, the Indonesian Ministry of Health will be able to more accurately and efficiently control infectious diseases and craft healthcare policies. Additionally, since pathogens do not respect regions or borders, the international community will benefit from an awareness of potential pandemic pathogens in Indonesia and the clinical knowledge generated by this study.

2. Aim and Objectives

2.1. Aim

To understand the scope of pathogens responsible for outbreaks and difficult clinical cases in Indonesia, and to characterize the clinical course of the diseases to better inform diagnostics, treatments, and prevention strategies.

2.2. Primary objective

To identify the causative agents and describe the clinical characteristics of presumptive infections reported during infectious diseases outbreaks or referred from difficult cases of unidentified etiology in Indonesia.

2.3. Secondary objectives

- To describe the disease course and case management of the presumptive infections
- To assess the accuracy of diagnostic tests of the presumptive infections
- To assess treatments and short-term outcomes of the presumptive infections
- To generate epidemiologic data to inform ongoing and future disease control and prevention efforts

3. Research Benefits

- This study offers no immediate or direct benefit to participants. Participants and their physicians may be provided the results of research tests, but any decisions related to disease diagnosis, case management, or treatment are made at the sole discretion of the attending clinician providing standard of care (SoC).

- This study will provide a better understanding of the causative agents, clinical characteristics, and epidemiology of reported infectious disease outbreaks and difficult cases of unidentified etiology in Indonesia.
- This study will generate data to support evidence-based recommendations to health authorities for disease diagnostics, treatment, and prevention.
- This study will improve the INA-RESPOND Network's capacity for conducting infectious disease research during dynamic outbreak scenarios, and it will strengthen the specialization of the Reference Laboratory to identify pathogens from very difficult cases of unidentified etiology.

4. Methods

4.1. Study Design

This is a study to identify causative agents and describe clinical characteristics of infectious disease outbreaks and difficult cases of unidentified etiology in Indonesia. It is a retrospective and prospective observational study with an exploratory design. There will be no intervention to the participants that is intended to affect their SoC or clinical outcome. An outline of the study flow is described in Section 4.3. General guidance on specimen types, collection, handling, and processing is described in Appendices 1 and 2. The study is registered on ClinicalTrials.gov with identifier NCT04339179.

Prospective study activities will be initiated upon official request from health authorities and health facilities/institutions. Requests are expected to be filtered through and evaluated by the **20** active INA-RESPOND Network sites before inclusion in the study. Cases will broadly fall into the two categories of difficult cases of unidentified etiology and outbreaks. For difficult cases, network sites, in consultation with the protocol core team, will first assess referred cases to determine whether they meet the criteria for inclusion in the study. If approved by the site's principal investigator (PI) and the study PI and Co-PIs, the cases will be included. A documented informed consent or assent from participants with parental/legally accepted representative (LAR) consent will be sought prior to enrollment and study procedures. Demographics, medical history, clinical data, and biological specimens will be collected at study visit 1 (baseline visit at Day

0), and clinical data and biological specimens will be collected one time at study visit 2 (follow-up visit between Day 7-14), as well as at any necessary study visits after Visit 2. **Blood samples (5-15 mL) and clinically indicated non-invasive samples such as sputum, urine, stool, nasopharyngeal swab, etc., will be collected from all participants at each study visit, when possible. If there is a risk to the participant's safety, such as a bleeding disorder, or if the maximum allowable limits for sample collection have been reached by SoC procedures or other studies, then samples will not be collected.** Specimens collected under SoC visit(s) could be included in the study if leftover specimen material is shared by the attending clinician. **Clinical data collected as part of SoC visit(s) could also be included in the study if shared by the attending clinician. If SoC visits and procedures occur between study visits, the data and leftover specimens shared with the study from these visits and procedures will be considered as part of interim visits. These interim visit(s) are independent of the study and may or may not occur depending on SoC.** Whenever possible, any specimen material remaining after study testing is complete will be cryopreserved and stored indefinitely for future research such as, but not limited to, developing and validating diagnostic tests, determining the evolution of pathogens, and determining host disease susceptibility.

For outbreak cases, relevant site PIs and the study PI and Co-PIs will communicate closely with health authorities to determine how cases should be included in the study. Other subject matter experts and institutions may be consulted on a case-by-case basis. When cases are approved for study inclusion, data and specimen collection will be guided by the health authorities and may differ from data and specimens collected during difficult cases. A documented study informed consent will be sought from participants whenever possible, in addition to copies of any forms collected by the health authorities that have been signed by participants or their LAR. If the study team is unable to obtain a documented informed consent for reasons other than the patient declining participation in the study, the patient can still be enrolled in the study in a de-identified manner. The de-identification process will begin with the MoH, who is the sole owner and steward of clinical information collected during outbreak investigations. Given the obligation of the MoH to maintain patient

privacy, complete patient data will not be shared directly with INA-RESPOND or third parties for de-identification. Instead, MoH officials and the core study team will jointly review the general data collection form developed and implemented by the MoH for that individual outbreak. With consideration for the circumstances of the individual outbreak, appropriate data variables that cannot collectively be used for identification will be determined and agreed upon, with the final decision being left to the MoH. Any data collected by health authorities will then be scrubbed of personally identifiable information (PII) so that only the agreed upon variables are shared with the study team. Samples collected during outbreaks and from difficult cases of unknown etiology will be analyzed at the INA-RESPOND Reference Laboratory at their own pace. Results from any research tests will be shared with the requesting authorities as research-use-only and are not intended to alter SoC. Upon approval from the relevant health authorities, any specimen material remaining after study testing is complete will be cryopreserved and stored indefinitely for future research such as, but not limited to, developing and validating diagnostic tests, determining the evolution of pathogens, and determining host disease susceptibility.

Retrospective study activities will be ongoing throughout the duration of the study. The INA-RESPOND Reference Laboratory will perform research tests on various specimens collected as part of historical outbreaks and previous difficult cases where an etiology was never identified in order to identify the causative pathogen. Like the prospective arm of the study, retrospective cases will be evaluated by the study PI and Co-PIs to determine whether or not to include them in the study. If included, cases will be enrolled in a de-identified manner since obtaining informed consent is not possible. When the MoH is the owner of the samples and associated clinical data, the de-identification process described above will be followed. When the samples and associated clinical data are owned by another party, such as a university or private research entity, the core study team will jointly review the general data collection form used when the samples and data were originally collected. With consideration for the circumstances of the study or situation under which the data was collected, appropriate data variables that cannot collectively be used for identification will be determined and

agreed upon, with the final decision being left to the party of primary ownership. Samples and available, scrubbed metadata will then be obtained and analyzed.

Depending on the complexities of the cases referred to this study, more detailed study plans, procedures, and CRFs may be developed, including specific or additional laboratory procedures not described in the Appendices 1 and 2. The plan will be written as an additional document (annex) to this general protocol, and the IRB will be notified.

4.2. Sample Size and Study Duration

The ORCHID study is an observational study with exploratory design to identify pathogenic etiology in outbreaks or difficult cases. There is no minimum number of cases that must be recruited in this study since the study is a 5-year open protocol to respond to research needs in outbreaks or difficult cases. The characteristics of the research is continuous and immediately adapts to current situation. The estimated sample size in the protocol is the upper limit of subjects that can be recruited for the study, based on the resources and capacity of the INA-RESPOND network to fulfil the primary and secondary objectives of the study properly.

This is a 5-year study that will enroll an estimated total of 2,000 prospective cases, with a ceiling of 4,000 cases if necessary. **The subjects as prospective cases will be recruited directly at the research site (in person visit), both in outbreak situations and difficult clinical cases.** It is anticipated that all 19 INA-RESPOND sites across Indonesia will participate in the study, which would result in approximately 21 patients enrolled per site per year. The study will also include an estimated total of 500 retrospective cases, with a ceiling of 1,000 cases if necessary. **The retrospective cases come from the stored specimen at the site in which the etiology is to be determined.**

This study is designed to capture a broad range of diseases instead of a specific disease or subset of diseases. Dengue fever and typhoid fever are highly prevalent in Indonesia, but this study includes criteria to screen out dengue and typhoid in favor of less common and less understood diseases, such as rickettsiosis, leptospirosis, chikungunya, and hanta virus infection. Prevalence

estimates of these diseases in Indonesia are very poor and frequently unreliable. Consequently, the study sample size has been determined based on resource availability and INA-RESPOND Reference Laboratory capacity rather than expected disease prevalence or anticipated cases of a particular disease.

This study is not meant to stand alone as a definitive survey of the distribution of causative agents of disease in Indonesia. The population from which samples are drawn from is likely to vary over both time and site, and testing methodology for each sample will be clinically informed and unlikely to follow a common algorithm. Thus, the data collected during this study is not intended to be analyzed completely together, as it will likely represent a dynamic mix of different populations.

In the scenario that data from this study – or more likely, a subset of data from this study – is suitable for analysis, Table 1 summarizing the necessary sample size for estimating the prevalence of a generic binary outcome over a range of desired precision (+/-) and true underlying prevalence assumptions can be utilized. For example, with a true prevalence of 0.10 and a desired precision of 0.02 (i.e. 95% confidence interval with a width of 0.04), one would require a sample size of 865.

Table 1 Required sample size for estimating the prevalence of a generic binary outcome over a range of desired precision and true underlying prevalences

		True prevalence					
		0.01	**0.02**	**0.05**	**0.10**	**0.20**	**0.50**
Desired precision (+/-)	**0.01**	381	753	1825	3458	6147	9604
	0.02	96	189	457	865	1537	2401
	0.05	16	31	73	139	246	385
	0.10	4	8	19	35	62	97
	0.20	1	2	5	9	16	25

4.3. Overview of the Study Flow

4.3.1. Prospective Study

4.3.1.1. Ongoing Patients with Difficult Infections of Unidentified Etiology

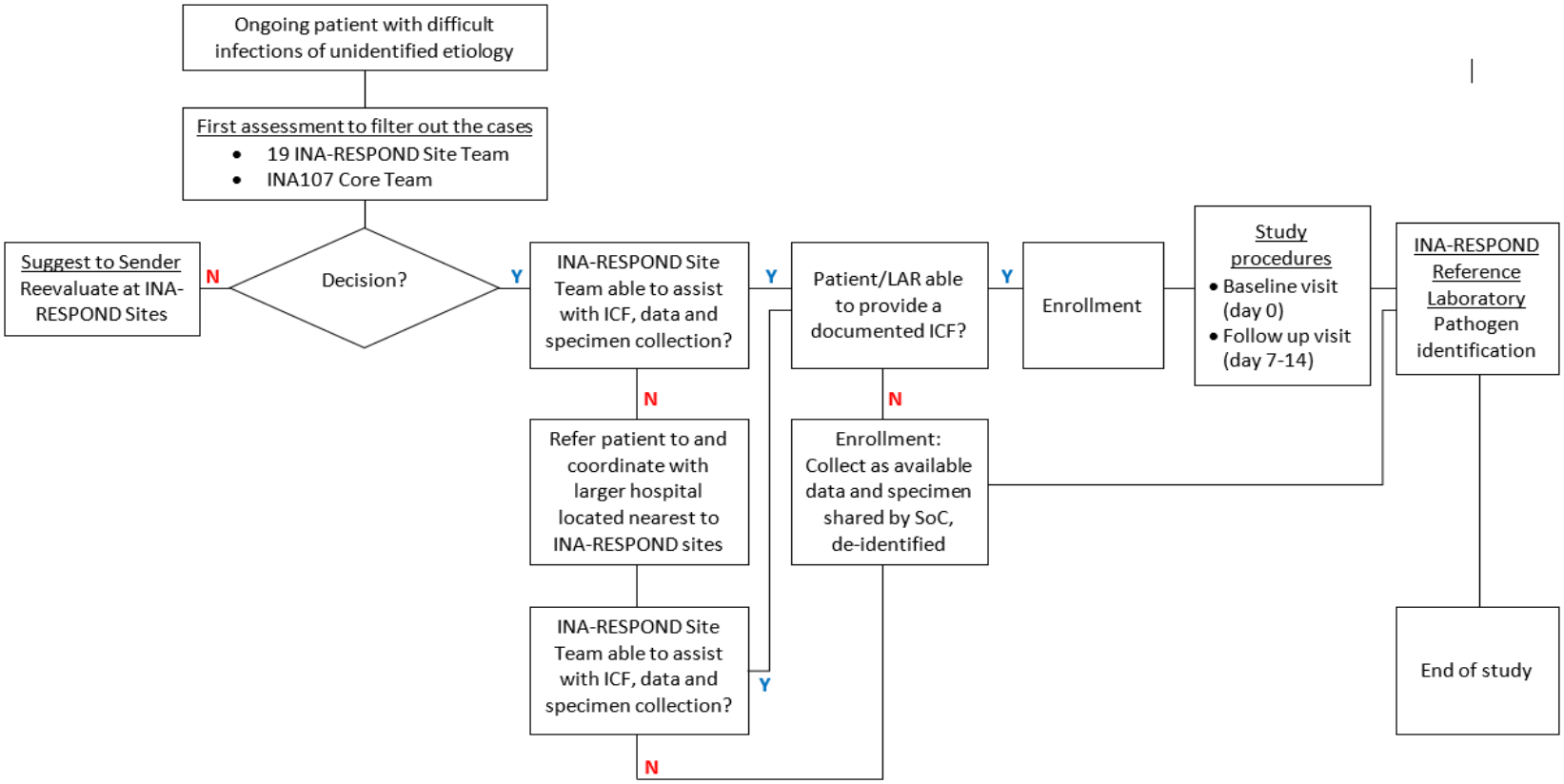

Figure 1 Study flow for prospective study to ongoing patients with difficult infections of unidentified etiology

4.3.1.2. Ongoing Patients in Outbreak Situations

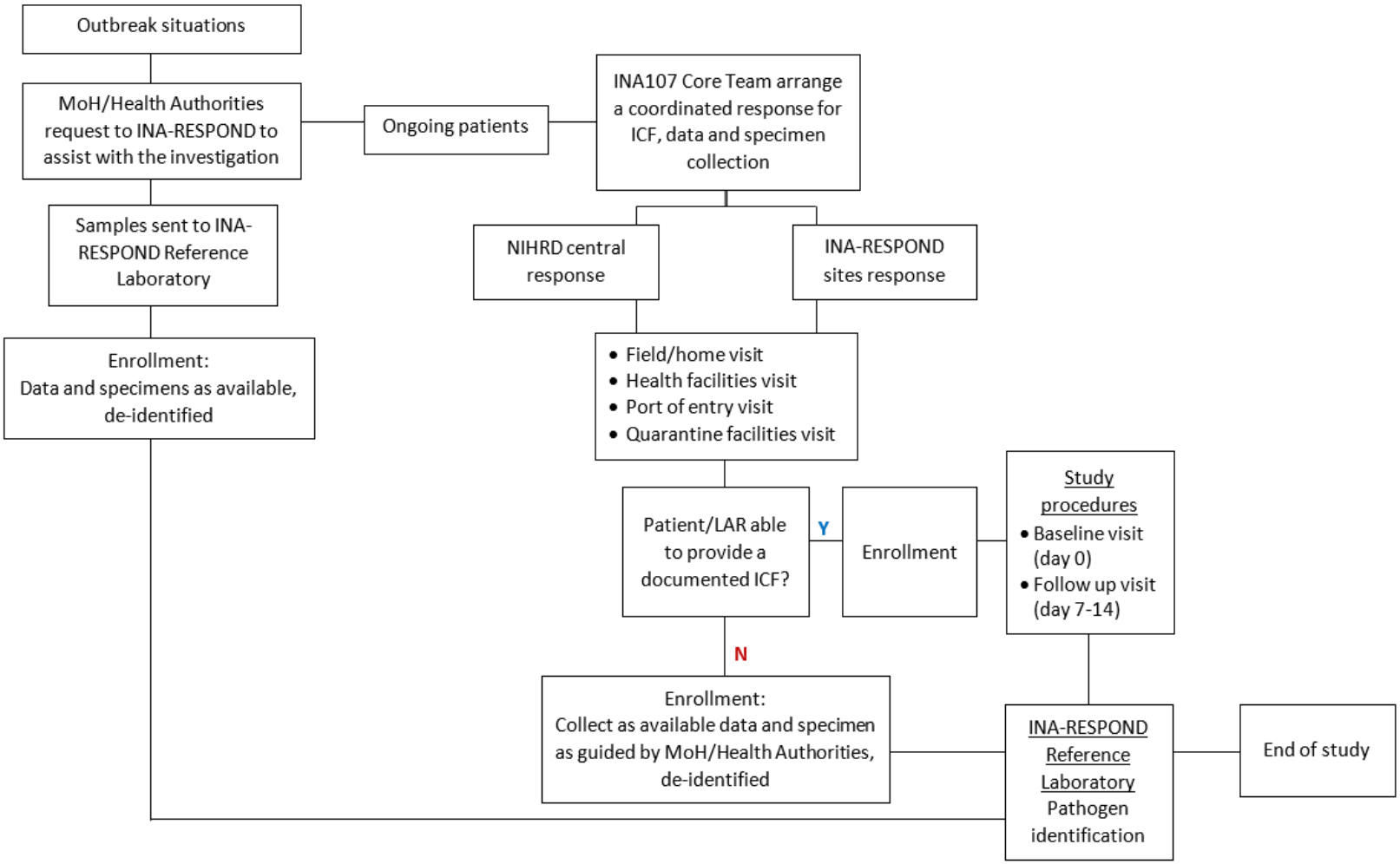

Figure 2 Study flow for prospective study to ongoing patients in outbreak situations

4.3.2. Retrospective Study

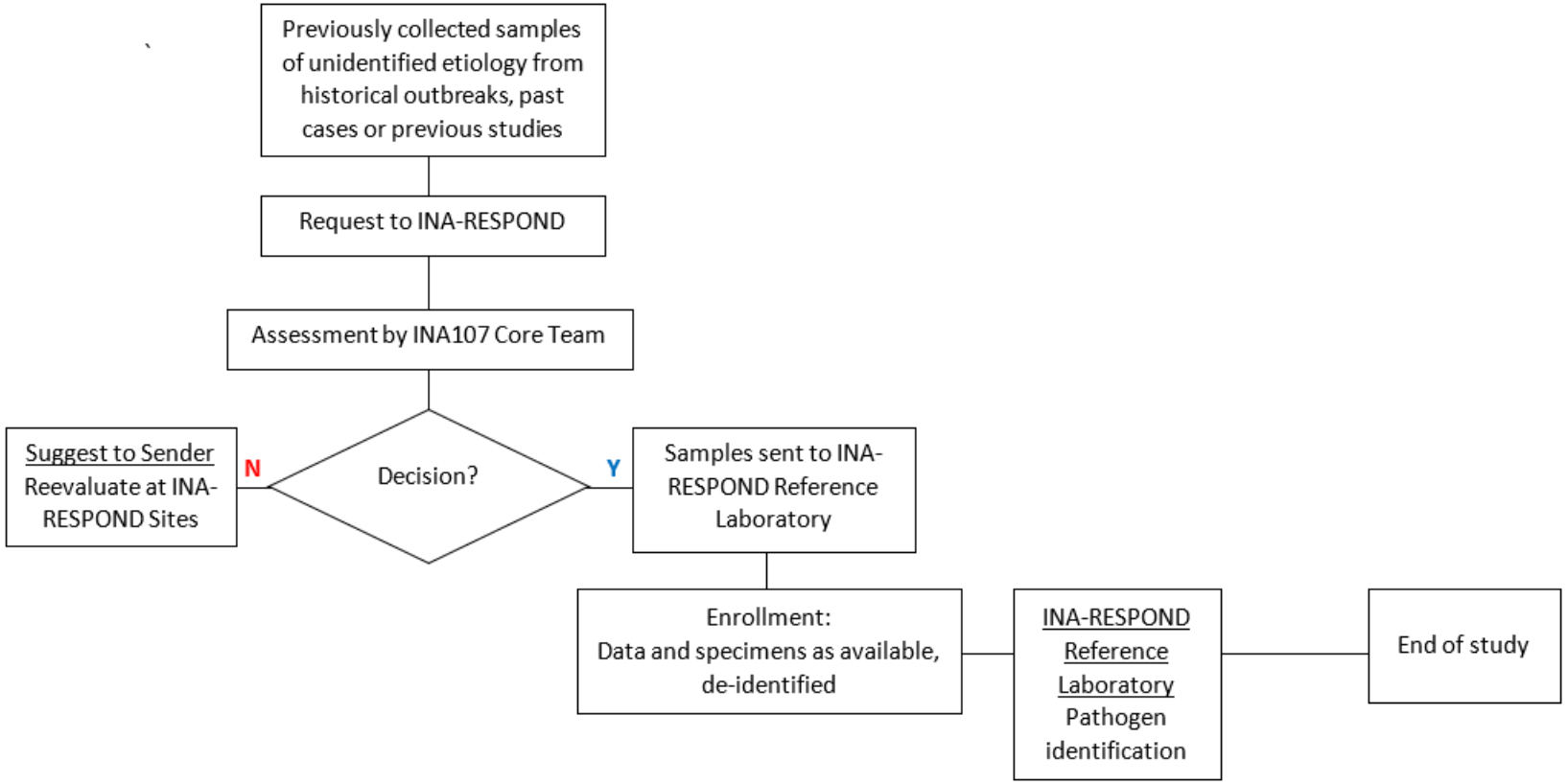

Figure 3 Study flow for retrospective study to previously collected samples

4.4. Study Instruments

The following instruments will be used in this study:

a. Forms
   - Study informed consent (for prospective investigation)
   - Screening log
   - Enrollment log
   - Case Report Forms
   - Electronic data capture systems

b. INA-RESPOND data and specimen database

c. INA-RESPOND electronic document management system (EDMS)

4.5. Prospective Study

4.5.1. Eligibility Criteria

4.5.1.1. Ongoing patients with difficult infections of unidentified etiology

4.5.1.1.1. Inclusion

1. Adult or child of any age hospitalized with a current episode of illness with a presumed infectious disease of unidentified etiology
2. Negative for Dengue virus infection by an antigen-based and antibody-based diagnostic test (i.e. NS1 antigen test and Dengue-specific IgM test)
3. Negative for *Salmonella* Typhi infection by Standard of Care testing (i.e. blood culture, Widal test, or Tubex rapid test)
4. Able to provide a documented informed consent
5. Agrees to the collection and storage of specimens for laboratory testing and/or future research (participants may decline storage of specimens for future research)

4.5.1.1.2. Exclusion

1. Investigators' discretion for patient safety and wellbeing

4.5.1.2. Ongoing patients in outbreak situations

4.5.1.2.1. Inclusion

1. Adult or child of any age undergoing a current episode of illness with a presumed infectious disease of unidentified etiology
2. Referral from the MoH as part of a suspected or identified outbreak of infectious disease

4.5.1.2.2. Exclusion

1. None

4.5.2. Visit Schedule and Procedures

Clinical and laboratory evaluations will be performed for each participant after they have provided a documented informed consent or assent with parental/LAR consent. If the study team is unable to obtain a documented informed consent for reasons other than the patient declining participation in the study, the patient can still be enrolled in the study in a de-identified manner. Any data collected by health authorities as part of SoC will be scrubbed of personally identifiable information (PII), such as date of birth, residence, and other variables that may vary depending on the circumstances and/or scale of the individual outbreak. Prior to receiving any patient data, the core study team will consult with the relevant health authorities to determine what metadata will be included with the de-identified samples.

See Appendices 1 and 2 for general specimen types and collection guidelines. A general study timeline for ongoing patients with difficult infections of unidentified etiology is shown in Figure 4.

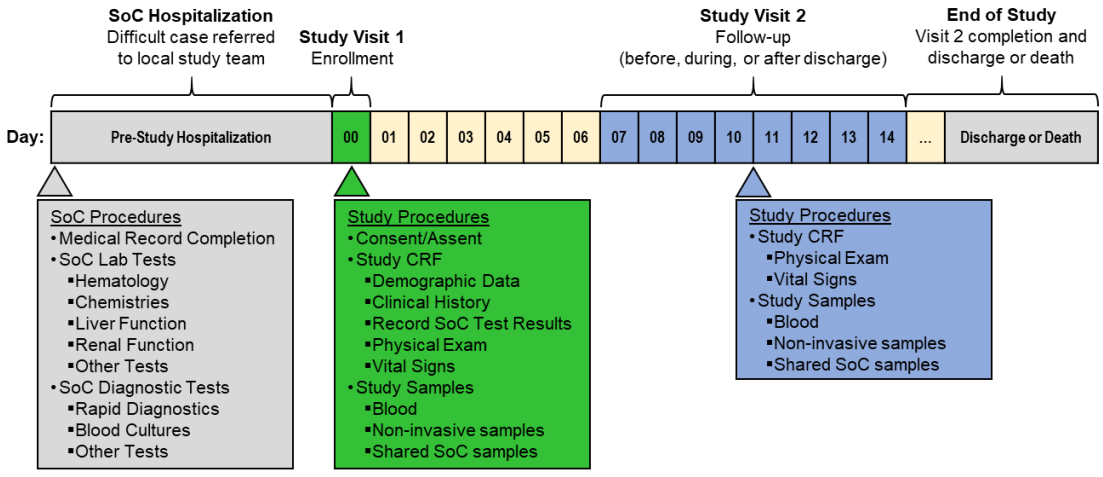

Figure 4 Study timeline for ongoing patients with difficult infections of unidentified etiology.

4.5.2.1. Study Visit 1: Enrollment and Baseline Visit (Day 0)

Eligibility of ongoing patients with difficult infections of unidentified etiology must be verified before evaluations begin at the baseline visit (Day 0). If the participant is found to be eligible and consents, the participant is considered enrolled in the study. Foreign, non-Indonesian patients may also be enrolled in the study, but if they return to their home country before study completion, only the follow-up visit will not be conducted. This will not be considered a protocol deviation.

The following procedures will be completed at the baseline visit (Day 0):

1. Demographics including, but not limited to: sex, age, residence, occupation.
2. Medical history including, but not limited to: travel history, human, insect and animal exposure, vaccination history, medication use prior to enrollment.
3. Clinical data including, but not limited to: current signs and symptoms, height and weight, vital signs, comorbidities, treatment, clinical outcome at this visit, available SoC laboratory or imaging results.
4. Specimen collection **(when possible)**: whole blood (5-15 mL) and clinically indicated non-invasive specimens such as sputum, urine, stool, nasopharyngeal swab, etc. Specimens collected under SoC can also be included in the study if leftover material is shared.
5. Laboratory testing: routine hematology, blood chemistry, liver function tests, and renal function tests.

4.5.2.2. Study Visit 2: Follow-Up Visit (Day 7-14)

The following procedures will be completed at the follow-up visit (one time between Day 7-14):

1. Clinical data including, but not limited to: current signs and symptoms, height (if previously not done) and weight, vital signs, comorbidities, treatment, clinical outcome at this visit, available SoC laboratory or imaging results.
2. Specimen collection **(when possible)**: whole blood (5-15 mL) and clinically indicated non-invasive specimens such as sputum, urine, stool, nasopharyngeal swab, etc. Specimens collected under SoC can also be included in the study if leftover material is shared.
3. Clinical outcome data at hospital discharge or death (when applicable).

4.5.2.3. Study Visits After Visit 2

Study visits **after Visit 2** may be necessary depending on the complexity of the ongoing case. Such cases could include those where convalescent specimens are needed to definitively identify an etiology, or those where long-term sequelae of interest are observed or anticipated. **If study visits after Visit 2 are needed**, then the following procedures will be completed:

1. Clinical data including, but not limited to: current signs and symptoms, height (if previously not done) and weight, vital signs, comorbidities, treatment, clinical outcome at this visit, available SoC laboratory or imaging results.
2. Specimen collection **(when possible)**: whole blood (5-15 mL) and clinically indicated non-invasive specimens such as sputum, urine, stool, nasopharyngeal swab, etc. Specimens collected under SoC can also be included in the study if leftover material is shared.
3. Clinical outcome data at hospital discharge or death **(when applicable).**

4.5.2.4. Interim Visits as part of Standard of Care

At any time between study visits, clinical data and leftover specimen material collected as part of SoC visits could also be included in the study if shared by the attending clinician. These interim visits are independent of the study and may or may not occur depending on SoC procedures.

4.5.3. End of Study Criteria

1. Completion of de-identified sample analysis
2. Hospital discharge after Visit 2
3. Completion of Visit 2 if discharged from hospital prior to Visit 2
4. Participant or parent/LAR withdraws study participation
5. Participant is lost to follow-up or moves away from the study area
6. Participant dies
7. Participant was inadvertently enrolled
8. Investigator determines that further participation would be detrimental to the health or well-being of the participant
9. The study is stopped for other administrative reasons

4.6. Retrospective Study

4.6.1. Eligibility Criteria

4.6.1.1. Inclusion criteria

1. Samples from an adult or child of any age who experienced a presumed infectious disease of unidentified etiology
2. Current episode of illness has ended

4.6.1.2. Exclusion criteria

1. Positive for Dengue virus infection, if results are available
2. Positive for *Salmonella* Typhi infection, if results are available

4.6.2. End of study criteria

1. Completion of sample analysis
2. Depletion of available samples

4.7. Defining Difficult Cases of Unidentified Etiology

While this study aims to assist clinicians at the hospitals when they have difficult infectious disease of unidentified etiology, it should be clear that this is a research study and not simply an advanced diagnostic laboratory. Sites may or may not receive etiology results before a patient is discharged

Several etiologies can only be confirmed using fresh specimens and culture, for example, blood culture for sepsis, and urine culture for urinary tract infection. Therefore, it is expected that clinicians have conducted the search of the pathogens based on the available facilities at their hospitals and/or diagnostic laboratories in their region. INA-RESPOND laboratory does not have the capacity to test for pathogens that only can be identified by these cultures.

Hospital should also take advantage of any other clinical testing they have on-site, such as microscopy or RDTs, so that the patient receives the fullest possible benefit. For screening dengue, sites should test for NS1 and IgM/IgG antibody using at least rapid diagnostic test and for screening typhoid fever using blood culture or tubex (>=6). Although clinicians may not think of these diseases as the causes of the diseases, ORCHID requires these tests to ensure that our study is not flooded with dengue and typhoid

fever as it will reduce the essence of our aim. Furthermore, based on the AFIRE study, approximately 20% of unsuspected dengue at the hospitals were confirmed dengue at the reference laboratory.

To accommodate difficult cases that have not been screened for dengue and typhoid fever, sites can include these cases in the retrospective component of the study. After discussion with the team on site and INA-RESPOND secretariat, and approval from the chair of INA-RESPOND, specimens can be stored at INA-RESPOND sites and sent to INA-RESPOND laboratory on a regular basis. However, since retrospective samples will not come with the detailed CRF data that the difficult case samples come with, they are less ideal. There are also fewer retrospective case spots in the study, and the selection process for those samples will naturally be much more stringent.

5. Specimen Collection and Testing

Specimens included in this protocol will vary depending on the source of the participants. For ongoing patients with difficult infections of unidentified etiology, all specimens will be collected and handled at each study site by laboratory personnel or designees. Appropriate precautions will be determined and followed by all personnel in drawing, handling, transporting, and storing of all biological specimens. Specimens will be labelled accurately and legibly with a unique identifier/code that does not contain any information capable of directly linking the specimens to the study participants. Specimens will be logged and tracked using an electronic specimen tracking/database system, and only authorized personnel will have access to the participant code and the samples.

For ongoing patients in outbreak situations, specimens will be received from designated Ministry of Health authorities **unless MoH authorities refer participants to the study team to be seen**. Specimen type determination and collection will occur independently of the study at the judgement of the health authorities **unless MoH authorities refer participants to the study team to be seen**. It is expected that participants will provide sample collection consent to health authorities but will not be asked to provide study consent **unless the participants are seen by the study team**. Therefore, these participants will be

enrolled in a de-identified manner, where coded samples without an identifying key are provided to the INA-RESPOND Reference Laboratory for analysis. Appropriate precautions will be followed in the handling, processing, and storage of all biological specimens, and the de-identified specimens will be logged and tracked using an electronic specimen tracking/database system.

For previously collected specimens to be included in the retrospective arm of the study, specimen type determination and collection have occurred independently of the study. Unless documented informed consent permitting sample use in future research is obtained, these participants will be enrolled in a de-identified manner, where coded samples without an identifying key are provided to the INA-RESPOND Reference Laboratory for analysis. Appropriate precautions will be followed in the handling, processing, and storage of all biological specimens, and the de-identified specimens will be logged and tracked using an electronic specimen tracking/database system.

Etiology identification for all participants will occur at the INA-RESPOND Reference Laboratory. Other relevant clinical laboratory testing requiring freshly drawn samples can be completed at the INA-RESPOND study sites. The laboratory testing to be completed at the INA-RESPOND Reference Laboratory will focus on the identification and/or confirmation of suspected etiologic agents in order to meet the objective of the study. Additional, relevant exploratory activities may include, but are not limited to, research tests to: a) study immune markers that might enable better management or prediction of outcomes for patients, b) study pathogenicity, and c) identify genetic markers that may increases or decrease disease susceptibility. Routine laboratory tests may also be completed as needed. Whenever possible, any specimen material remaining after study testing is complete will be cryopreserved and stored indefinitely for future research such as, but not limited to, developing and validating diagnostic tests, determining the evolution of pathogens, and determining host disease susceptibility.

The sharing of samples and/or data with entities outside of the study will follow regulations established in Material Transfer Agreements (MTAs).

If the initial testing fails to identify the suspected etiology, the study core team may develop and suggest a clinically-informed algorithm for further testing to be completed with the remaining specimens (Figure 5).

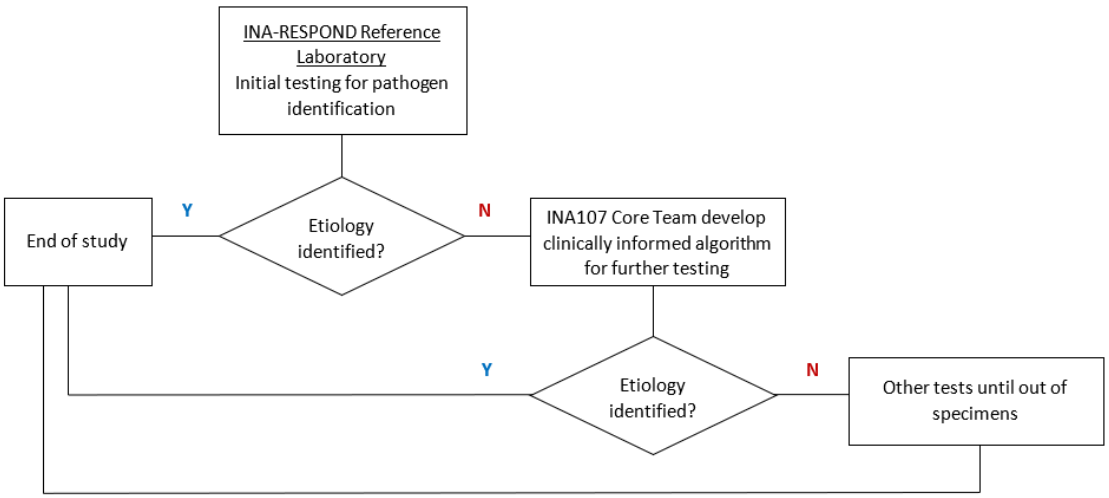

Figure 5 Flow of specimen testing at the INA-RESPOND Reference Laboratory

At the completion/termination of the study, specimens and data will either be destroyed or transferred to another existing protocol following approval from the INA-RESPOND Network Steering Committee and relevant IRBs. Any loss or unanticipated destruction of samples or data (i.e. due to freezer malfunction) that compromises the scientific integrity of the data collected for the study will be reported to the IRB.

The capacity of the INA RESPOND Reference Laboratory for pathogen identification will be described in Appendix 5.

6. Data management and Analysis

6.1. Data Management

For ongoing patients with difficult infections of unidentified etiology, participants will be coded with a unique identifier that does not contain any information capable of linking the data to the study participants. Only authorized personnel will have access to the participant code and the data. For ongoing patients in outbreak situations and retrospective patients, participants will also be coded with a unique identifier that does not contain any information capable of linking the data to the study participants. These participants will remain coded and de-

identified throughout the study since it is anticipated that study informed consent will not be obtained.

Data will be keyed and tracked using OpenClinica, RedCap, or other tools, as appropriate. Data will be periodically sent to the central data management center of INA-RESPOND and analyzed by the investigator team and approved partners. During the study and following study completion, data will be shared with the scientific community through peer-reviewed publications and presentations at local, national, and international meetings. IRB approval and approval from the INA-RESPOND Network Steering Committee must be sought prior to any sharing of data. Upon completion of the study, the final de-identified dataset will be made available to approved users under a specific data-sharing agreement as soon as possible, but no later than the acceptance for publication of the primary research manuscript. Any raw genome data and relevant associated metadata will be made available to the scientific community through submission to NCBI and appropriate databases such as GenBank. All study data will be shared in compliance with Indonesian legislation regarding the sharing of human participants data.

6.2. Analysis

Descriptive analyses will be performed, and data will be summarized using descriptive statistics along with appropriate distribution ranges. Continuous variables will be summarized using means and standard deviations for normally distributed variables, and medians and interquartile ranges for non-normally distributed variables. Categorical variables will be summarized with percentages in each category. Further specific and appropriate statistical analyses will be developed and applied as needed.

7. Tracking of Study Decisions

Each decision regarding the study plan, procedures, or analyses will be properly documented. This could include, for example, the determination of visit schedules, the decisions from laboratory evaluations and their underlying reasons, the rules for analyses, etc.

8. Assessment of Safety

8.1. Specification of Safety Parameters

Participant conditions may vary from healthy to complicated, with various underlying etiologies at baseline. Additionally, participant medical management will be SoC for those suspected illnesses and complications and will therefore not be part of the research process. Only Adverse Events (AEs) related to the research procedures, not the underlying disease states of the participants, will be followed in this protocol. Serious events not meeting the adverse event definition will be logged as Reportable Events (RE) and reported to the IRB within 10 working days of the investigator's awareness.

8.2. Adverse Events

An adverse event (AE) is any untoward or unfavorable medical occurrence in a human participant that occurs within 48 hours of study-related specimen collection (i.e. blood draw,) that is possibly, probably, or related to the specimen collection. Any event outside of this 48-hour window period will not be considered an AE for this study.

8.3. Serious Adverse Events

A serious adverse event (SAE) is defined as any AE that is possibly, probably, or definitely related to the research and meets one or more of the seriousness criteria below:

- results in death;
- is life-threatening (places the participant at immediate risk of death from the event as it occurred);
- results in inpatient hospitalization or prolongation of existing hospitalization;
- results in a persistent or significant disability/incapacity;
- results in a congenital anomaly/birth defect;
- results in important medical event based upon appropriate medical judgment that may jeopardize the participant's health and may require medical or surgical intervention to prevent one of the other outcomes listed in this definition.

Any event outside the AE definition that meet one/more of the seriousness criteria as mentioned above will be reported as Reportable Event (RE).

8.4. Unanticipated Problem

An unanticipated problem (UP) is defined as any incident, experience, or outcome that is defined as:

1. Unexpected in terms of nature, severity, or frequency in relation to:
    - the research risks that are described in the research protocol and informed consent document or other study documents; and
    - the characteristics of the participant population being studied; and
2. Related or possibly related to the participation in the research; and
3. Places participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized or is an SAE.

8.5. Non-Compliance

Non-compliance is defined as the failure to comply with applicable IRB requirements, or regulatory requirements for the protection of human participants. Non-compliance is further characterized as

3. Serious: Non-compliance that:
    - Increases risks or causes harm, to participants.
    - Decreases potential benefits to participants.
    - Compromises the integrity of the National Institutes of Health Human Research Protection Program (NIH-HRPP).
    - Invalidates the study data.
4. Continuing: Non-compliance that is recurring.
5. Minor: Non-compliance that, is neither serious nor continuing.

9. Safety Events Reporting

9.1. Expedited Reporting to IRB

Serious and non-serious UPs, serious or continuing non-compliance, and deaths will be reported within 10 working days of investigator awareness. SAEs that are possibly, probably, or definitely related to the research will be reported to the IRB within 10 working days of investigator's awareness, regardless of expectedness. REs will be reported annually to IRB.

9.2. Annual Reporting to IRB

The following items will be reported to the IRB in summary at the time of Continuing Review:

- All deaths.
- Summary of AEs, REs, SAEs, or Ups.
- Non-compliance.
- Any trends or events which in the opinion of the investigator should be reported.

10. Monitoring and Evaluation

The study will be conducted in compliance with this protocol, the International Conference on Harmonization (ICH) Guidelines for Good clinical Practice (GCP) and any applicable regulatory requirements. Independent monitors, under contract by the Sponsor, will visit the clinical research site to monitor the study implementation in accordance with the appropriate regulations. The details of monitoring visits will be described in Monitoring Plan (MP). The objectives of a monitoring visit, among others, will be:

1. To verify the consistency of each participant's records with the source documents.
2. To ensure the compliance of study procedures to the protocol.
3. To ensure the completeness and accuracy of records.
4. To verify the prompt reporting of all data points, including reporting SAEs.

The site investigator (or designee) will make the study documents (e.g., ICFs and CRFs) and pertinent hospital or clinical records readily available for inspection by the local institutional review board/ethics committee (IRB/IEC), the local and national regulatory authorities, and the site monitors for confirmation of the study data.

11. Human Participant Protection

11.1. Ethical Review

Prior to implementation, the study protocol or a more specific study plan or procedures and any written information to be provided to participants for this

study will be submitted for approval to the appropriate IRB. Records of the IRB review and approval of all the documents pertaining to the study will be kept on file by the site investigator and will be made available for inspection at any time during the course of the study. Continuing reviews, including a study progress report will be submitted according to the requirement of the appropriate IRB, but not less than once a year at a minimum.

11.2. Potential Risk and Benefit to the Participants

Potential risks will include, but not limited to:

- Risks inherent to specimen collection procedures, such as blood draw risk. The risks of blood drawing are minimal and consist of mild discomfort and or bleeding at the finger prick site, feelings of dizziness or faintness, bruising, swelling, and rarely fainting or local infection. Other risks will be detailed in the additional study plan/procedures that will be developed in response to the related outbreaks or referred infectious disease cases.

Potential benefits will include, but not limited to:

- Increasing health awareness. Participants may become more aware of their health, aided by contact by the study team to their doctor.
- Increasing access to health care. Participants may become more aware of services that are available for infectious diseases. They may also have easier access to such services, by virtue of being integrated into the health care system.

11.3. Participant Reimbursement

Participant time and transportation cost to participate in the study will be reimbursed in accordance with the IRB approval.

11.4. Special Population

Pregnant and lactating women, adolescents, children of any age will be included in this study as needed. They will be managed according to the standard of care. There will be no investigational treatment or intervention assigned by this study. The study site team will ensure that their participation remains voluntarily without being coercive. The participants may withdraw participation from the study at any time for any reason.

11.5. Informed Consent

Informed consent is a process in which information is presented to enable persons to voluntarily decide whether or not to participate as a research participant. It is an ongoing conversation between the human research participant and the researchers covering the essential information about the study which begins before consent is given and continues until the end of the participant's involvement in the research.

Informed consent forms (ICFs) describing in detail the purpose of the study, duration, procedures, alternatives, risks, and benefits are given to the participant and a documented informed consent is required prior to starting any study procedures. ICFs will be IRB-approved and the participant will be asked to read and review the document. Participants will have the opportunity to ask questions about the study and have their questions answered. The participants should have the opportunity to discuss the study with their surrogates or think about it prior to agreeing to participate. The participants may withdraw from study participation at any time throughout the course of the study. The rights and welfare of the participants will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study**. In this study, participants may decline to have specimens stored for future research and/or genetic testing.**

Literate participants will document their provision of informed consent by signing their ICF. In case of illiterate participants, an oral consent will be obtained. The investigator or designee that perform the oral consent will sign and date the ICF. An impartial literate witness should be present during the entire informed consent discussion and should sign and date the ICF. The illiterate participants will be asked to document their informed consent by marking their ICF with a thumbprint in the presence of a literate witness.

In case of minor participants, assent with parental or legally accepted representative (LAR) consent will be obtained and documented from those who are capable of providing assent. Informed consent for those under the age of consent will be provided by their parents/LAR. Once the child reaches the age of consent, they will be re-consented to this study.

In case of severely ill participants, informed consent will be obtained by LAR (Legally Authorized Representative) and at first opportunity of well episode, the participant will be reconsented.

11.6. Premature Withdrawal of a Participant from Study Participation

Participants may voluntarily withdraw from the protocol at any point in the study. Attempts will be made to determine the reason that the participant wishes to withdraw.

11.7. Participant Confidentially

All records will be kept confidential to the extent provided by the law. Records will be kept in a locked cabinet, and all computer entry and networking programs will be done with coded numbers only. Hospital information, attributable to the participant, will not be released without written permission of the participant, except as necessary for monitoring, the IRB/IEC, or Office for Human Research Protections (OHRP). The study monitors and other authorized representatives may inspect all documents and records required to be maintained by the site investigator, including, but not limited to, medical records. The results of the research study may be published according to the INA-RESPOND policy, but participant names or identities will not be revealed.

12. Principal Investigator Curriculum Vitae

DONA ARLINDA

Name	:	Dona Arlinda
Sex	:	Female
Date of birth	:	05/December/1979
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Email	:	arlindona@ina-respond.net arlindona1@gmail.com arlindona@litbang.depkes.go.id
Language	:	English (Professional level) Bahasa Indonesia (Native)

Education

2019	**Thammasat University** *M.Sc., Bioclinical Science (Pharmacology and Toxicology)*	Bangkok, Thailand
2003	**Universitas Indonesia** *MD.*	Indonesia
2001	**Universitas Indonesia** *Bachelor of Medicine*	Indonesia

Work

2011 – present	**National Institute of Health Research and Development (NIHRD), Ministry of Health of Indonesia** Gedung 3 Lantai 1 Badan Litbangkes, Kementerian Kesehatan RI Jalan Percetakan Negara No. 29, Jakarta, Indonesia – 10560 Phone: +62-21-4244375 *Researcher*	Jakarta, Indonesia
2003 – 2011	**Medical Emergency Rescue Committee (MER-C)** Jalan Kramat Lontar No. J-157 Paseban, Jakarta, Indonesia – 10440 *General Practitioner*	Jakarta, Indonesia
2003 – 2011	**Allia Health Clinic** Jalan Limo Raya, Kota Depok, Jawa Barat, Indonesia *General Practitioner*	Depok, Indonesia

Trainings/Conferences/Seminars

2019	**Indonesia Research Partnership on Infectious Diseases (INA-RESPOND)** *Protocol Writing Workshop*	Jakarta, Indonesia
2018	**Indonesia Research Partnership on Infectious Diseases (INA-RESPOND)** *HIV Training*	Jakarta, Indonesia
2018	**Indonesia Research Partnership on Infectious Diseases (INA-RESPOND)** *Research Ethics Workshops*	Jakarta, Indonesia
2018	**Indonesia National Agency of Drug and Food Control** *Good Clinical Practice*	Jakarta, Indonesia
2017	**International AIDS Society (IAS)** *9th IAS Conference on HIV Science*	Paris, France
2017	**International Antiviral Society – USA** *Conference on Retroviruses and Opportunistic Infections* (CROI)	Seattle, USA
2016	**American Thorasic Society (ATS) – Indonesian Society of Respirology** *Methods in Epidemiologic, Clinical and Operations Research* (MECOR)	Jakarta, Indonesia
2015	**Nagasaki University** *Product Research and Development Course*	Nagasaki, Japan
2015	**Faculty of Medicine Universitas Gadjah Mada – WHO Tropical Disease Research (TDR)** *Good Clinical Laboratory Practice*	Yogyakarta, Indonesia
2014	**Forum for Ethical Review Committees in the Asian & Western Pacific Region (FERCAP) – Thammasat University** *Research Ethics and Responsible Research Course*	Bangkok, Thailand
2014	**Southeast Asian Ministers of Education Regional Centre for Food and Nutrition (SEAMEO-RECFON)** *Research Methodology Course*	Jakarta, Indonesia
2014	**Indonesia Research Partnership on Infectious Diseases (INA-RESPOND)** *Manuscript Writing Workshop*	Jakarta, Indonesia
2013	**Southeast Asian Ministers of Education Regional Centre for Food and Nutrition (SEAMEO-RECFON)** *Biostatistics Course*	Jakarta, Indonesia
2011	**Indonesian Clinical Epidemiology and Evidence Based Medicine (ICE-EBM) Network** *Basic Concept of Evidence-Based Medicine Workshop*	Jakarta, Indonesia

Research Experience

2018 – present	**Indonesia Research Partnership on Infectious Diseases (INA-RESPOND)** *D2EFT-Indonesia Research Project Coordinator* Dolutegravir and Darunavir Evaluation in adults Failing Therapy	Jakarta, Indonesia
2018 – present	**Indonesia Research Partnership on Infectious Diseases (INA-RESPOND)** *Schistosomiasis Research Project Coordinator* Validation of the Schistosomiasis Point-of-Care Circulating Cathodic Antigen (POC-CCA) Rapid Urine Test for Qualitative Detection of *Schistosoma japonicum*	Jakarta, Indonesia
2017 – present	**Indonesia Research Partnership on Infectious Diseases (INA-RESPOND)** *HIV Research Project Coordinator* A Prospective Observational Cohort on HIV Infection and Risk-Related Coinfections/Comorbidities (INA-PROACTIVE)	Jakarta, Indonesia
2015 – 2017	**National Institute of Health Research and Development (NIHRD) – Thammasat University** *Principal Investigator* Validation and Application of a Liquid Chromatography/ Tandem Mass Spectrometry (LC-MS/MS) Assay for Quantification of Dihydroartemisinin and Piperaquine in Plasma of Healthy Adults	Jakarta, Indonesia
2014 – 2016	**National Institute of Health Research and Development (NIHRD)** *Co-Investigator* Hospital-based Tuberculosis-Diabetes Registry in Indonesia	Jakarta, Indonesia
2013 – 2014	**National Institute of Health Research and Development (NIHRD)** *Principal Investigator* Systematic Review and Meta-Analysis of Inhaled Combination Therapy of Budesonide+Formoterol Versus Fluticasone+Salmeterol in Asthma	Jakarta, Indonesia
2013 – 2014	**National Institute of Health Research and Development (NIHRD)** *Principal Investigator* Literature Review of Frambusia: A Neglected Tropical Disease	Jakarta, Indonesia
2012 – 2013	**National Institute of Health Research and Development (NIHRD)** *Principal Investigator* Management of Type 2 Diabetes Mellitus in Primary Health Centers in Depok, West Java, Indonesia	Jakarta, Indonesia
2012 – 2014	**National Institute of Health Research and Development (NIHRD)** *Co-Investigator* Hospital-based Stroke Registry in Indonesia	Jakarta, Indonesia
2011 – 2012	**National Institute of Health Research and Development (NIHRD)** *Technical Coordinator, Baubau District, South-East Sulawesi* National Health Facilities Research	Jakarta, Indonesia

Publication

2018	**Indonesian Society of Tropical and Infectious Diseases** *Oral presentation* HIV Infection in Hospitalized Patients with Acute Fever in Indonesia	Bandung, Indonesia
2018	***Lembaga Penerbit Badan Penelitian dan Pengembangan Kesehatan*** *Book* *Panduan Penulisan Ilmiah* (A Guide to Scientific Writing)	Jakarta, Indonesia
2018	**International Conference on Interdisciplinary Academic Research and Innovation (IARI)** *Proceeding* Establishment of a Liquid Chromatography/Tandem Mass Spectrometry (LC-MS/MS) Assay for Quantification of Dihydroartemisinin in Plasma for Monitoring of Antimalarial Resistance in Indonesia	Banjarmasin, Indonesia
2017	**International Conference on Global Health (ICGH)** *Poster presentation* Assessment of Hospital Readiness for a Prospective Observational Cohort Study on HIV Infection and Related Coinfections/Comorbidities in Indonesia	Jakarta, Indonesia
2017	***Media Litbangkes*** *Journal article* *Perbedaan Faktor Sosiodemografi Dan Status Gizi Pasien Tuberculosis Dengan Dan Tanpa Diabetes Berdasarkan Registry Tuberkulosis-Diabetes Melitus 2014* (Differences in Sociodemographic Factors and Nutrition Status of Tuberculosis Patients With and Without Diabetes based on Tuberculosis-Diabetes Mellitus Registry 2014)	Indonesia
2017	***Media Litbangkes*** *Journal article* *Pengaruh Diabetes Melitus terhadap Gambaran Klinis dan Keberhasilan Pengobatan Tuberkulosis di Tujuh RSU Kelas A dan B di Jawa dan Bali* (The Effects of Diabetes Mellitus to Clinical Characteristics and Successful Treatment of Tuberculosis in Seven Public Hospitals Class A and B in Java and Bali)	Indonesia
2017	**American Society of Tropical Medicine and Hygiene (ASTMH)** *Oral presentation* Unfavorable Tuberculosis Outcome Associated with HIV, Drug Resistance, and Previous Treatment in Indonesia	Baltimore, USA
2016	**Asia Pacific Federation of Pharmacologists (APFP)** *Poster presentation* High Performance Liquid Chromatographic Method for the Determination of Piperaquine in Plasma	Bangkok, Thailand
2016	**American Thoracic Society (ATS)** *Poster presentation* Negative Interaction of Diabetes Mellitus with Clinical Characteristics and Treatment Success of Tuberculosis in Indonesia	San Francisco, USA
2015	***Lembaga Penerbit Badan Penelitian dan Pengembangan Kesehatan*** *Book*	Jakarta, Indonesia

Kajian Penyakit Menular Neglected dan Non-Neglected
(Literature Review of Neglected and Non-Neglected Infectious Diseases)

2014 ***Buletin Penelitian Kesehatan*** Jakarta, Indonesia
Journal article
Proporsi Seksio Sesarea dan Faktor yang Berhubungan dengan Seksio Sesarea di Jakarta
(The Proportion of Caesarean Section and Associated Factors in Hospital of Jakarta)

RETNA MUSTIKA INDAH

Basic Information

First name	:	Retna
Middle name	:	Mustika
Last name	:	Indah
Gender	:	Female
Place of Birth	:	Jakarta
Date of Birth	:	8/21/1983
Office Address		
- Institution	:	Puslitbang Sumber Daya dan Pelayanan Kesehatan Badan Penelitian dan Pengembangan Kesehatan
- Street	:	Jln. Percetakan Negara no. 29
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Home Address		
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- City	:	Jakarta Utara
- Province	:	DKI Jakarta
- Postal code	:	14230
Home telephone	:	-
Personal email address	:	retnaindah.sugiyono@gmail.com

Education

- Faculty of Medicine, Trisakti University (2000 – 2008)
- Master of Health Economic, University of Indonesia Public Health Programme (2014 – 2017)

Research Experiences

- Hospital Coordinator for Solidarity Trial, Clinical Trial of COVID treatment (2020)
- PROACTIVE (A Prospective Observational Cohort Study On Hiv Infection And Risk Related Coinfections/ Comorbidities In Indonesia) study protocol core team (2018 -2020)
- TRIPOD (TB Study of INA RESPOND on Drug Resistance) study protocol core team (2015 -2020)
- Hospital coordinator Indonesian Disease Registry (www.ina-registry.org) (2011 - 2016)
- DSMB secretary for High dose rifampicin for treatment of adults with tuberculosis meningitis (TBM): a
- dose finding study (ReDEFINe), 2014-2015
- District coordinator of National Non-Communicable Research, Ministry of Health Republic of Indonesia, 2015
- District coordinator of National Basic Health Survey, Ministry of Health Republic of Indonesia, 2013

- District coordinator of National Health Facilities, Ministry of Health Republic of Indonesia, 2011
- Attending physician in Wahana Clinic (Private Primary Health Care) in Jakarta (2009 - 2010)

Professional Training

- Good Clinic Practice Course & Workshop, IASMED (April 2020)
- Understanding The Process and Research Implementation of The Health Policy, University of Gadjah Mada (November 2016)
- Methods in Epidemiologic, Clinical and Operations Research (Level 2), American Thoracic Society (October 2018)
- Methods in Epidemiologic, Clinical and Operations Research (Level 1), American Thoracic Society (October 2015)

Publications

- Article, Building capacity for advances in tuberculosis research; proceedings of the third RePORT international meeting (2018)
- Book, Manuscript Writing Guidelines, Published by NIHRD (2017)
- The Effects of Diabetes Mellitus to Clinical Characteristics and Successful Treatment of Tuberculosis in Seven Public Hospitals Class A and B in Java and Bali Published by NIHRD Media, 2017
- Article, Differences of Sociodemography Factors and Nutrition Status of Tuberculosis Patients with and Without Diabetes Based on Tuberculosis-Diabetes Mellitus Registry 2014 Published by NIHRD Media, 2017
- Abstract, Indonesia Tuberculosis-Diabetes Registry: Comparison of Sputum Smear and Culture Results for Tuberculosis Diagnosis in Patients with and without Diabetes comorbidity for the 47th Union World Conference on Lung Health, Liverpool, 2016
  Challenge on Tuberculosis Infection Control in Indonesia: High Close Contact History in
- Abstract, Tuberculosis Patients with HIV and Diabetes Mellitus, ATS 2016 International Conference, San Fransisco, 2016
- Article, A Glimmer of Hope for Tuberculosis Treatment, INA RESPOND News Letter (2015)
- Article, Drug Resistance as Barrier in Treatment for Prevention, INA RESPOND News Letter (2015)
- Article, Tobacco Smoking: New Leader to Tuberculosis Jeopardy, INA RESPOND News Letter (2015)

13. Appendix 1. General Guidance on Specimen Types

Cases with Major Symptoms Criteria	**Sample Type**								
	Serum Acute **(Day 0-14)**	Serum Convalescent **(after day 14)**	Whole blood EDTA	Liquid Cerebrospinal (LCS)	Oropharingeal/ Nasopharingeal swab)	Sputum	BAL	Stool/ Rectal swab in VTM	Urine
1.Respiratory infection	√	√			√	√	√		
2.Central Nervous System (CNS) infection	√	√	√	√		√	√	√	
3.Diarrhea	√	√			√			√	
4.Hepatobiliary or UTI (leptospirosis, Hantavirus and Hepatitis A/B/C/E)	√	√	√						√
5. Unknown Fever or Fever with rash/hemorrhagic, or arthritis (up to 15 bacterial and virus panel) suspected as dengue like ilness/Chikungunya infection.	√	√	√						√
6. Unknown Fever or Fever with rash suspected for measles, HFMD/enterovirus infection.	√	√			√			√	
7. Unknown Fever	√	√	√	√	√	√	√	√	

14. Appendix 2. General Guidance on Specimen Collection, Handling and Processing

SPECIMEN COLLECTION GUIDELINES

Purpose of this document

The purpose of this document is to provide general specimen collection guidelines for healthcare providers and public health staff during an outbreak when the pathogen is unknown. The specimens listed in this document are those that may need to be collected to detect the etiologic agent during outbreak. When a specific pathogen is known or very strongly suspected, specimen collection should be tailored to the pathogen.

Reference Testing

Testing will be conducted by INA-RESPOND reference laboratories

General principles

1. Integrated approach.

These guidelines are designed for use in an outbreak setting where the etiologic agent is unknown. Sensitive assays should allow for an efficient and coordinated approach to specimen collection and diagnostic testing to evaluate multiple potential viral, bacterial or fungal etiologies. Each pathogen requires a unique set of specimen types, collection methods and handling conditions to optimize diagnostic yield. Because these guidelines are designed for detection of multiple pathogens, the sensitivity of detection of any one agent may be compromised. If a particular agent is strongly suspected, please refer to 1 pathogen-specific materials. To rule out other pathogens, multiple specimens may be necessary.

2. Recommended specimens

A. Respiratory specimens
   a. Nasal (N), Nasopharynx (NP) and Oropharynx (OP)
   b. Nasopharyngeal wash aspirate
   c. Sputum or induced sputum
   d. Tracheal aspirate
   e. Bronchoalveolar lavage (BAL) fluid
   f. Pleural fluid

B. Blood Specimens
   a. Serum or Plasma
   b. Whole Blood
   c. Buffy coat

d. PBMC
e. Paxgene

C. Urine

D. Stool

E. Other body fluid
a. CSF
b. Acites
c. etc

3. Timing of specimen collection.

- Specimens should be collected as soon as possible in the course of the illness and before antimicrobic therapy begin, if possible. The likelihood of recovering most viruses and many bacteria diminishes markedly >72 hours after symptom onset and after the initiation of appropriate antimicrobial therapy.
- If possible, Acute specimens should be collected within 72 hours of symptom onset and no later than 7 days after onset. While convalescence specimens should be collected after 14 days of symptoms

4. Interpretation of results.

The interpretation of laboratory test results should take into account whether proper specimen collection and handling occurred prior to receiving the specimen in the laboratory and pathogen specific test sensitivities and concurrent treatment. Also, some pathogens colonize the upper respiratory tract (e.g. *S. pneumoniae* and Hib), or can cause asymptomatic or symptomatic infection (e.g. rhinovirus or coronavirus). Therefore, each laboratory result needs to be interpreted individually for each pathogen. Combining results from selected cases may significantly improve the overall specificity for identifying the predominant cause or causes of an outbreak.

Collection Specimens

A. Collection of upper respiratory Specimens

1. Nasal swabs, nasopharyngeal (NP) swabs and oropharyngeal (OP)

a. Optimal timing.

Acute specimens should be collected within 3 days of symptom onset and no later than 7 days from all patients meeting the case definition identified during

the outbreak, ideally prior to the initiation of antimicrobial chemoprophylaxis or therapy.

b. Swab types.

Use only sterile dacron or rayon swabs with plastic shafts or if available, flocked swabs. DO NOT use calcium alginate swabs or swabs with wooden sticks, as they may contain substances that inactivate some viruses and inhibit some molecular assays.

d. Collecting Nasal swabs

- Ask the patients to attempt to clear the discharge by “blowing” his/her nose into non-scented tissue paper. (Allow one attempt.)
- Assist children whenever necessary.
- Do not try to clear the discharge with swabs, as this might be excessively traumatic.
- Insert swab into the nares
- Insert the swab approximately 2 cm (approximately ¾ inches) into the naris.
- Rotate the swab against the anterior nasal mucosa for 3 seconds.
- Using the same swab, repeat for other naris.
- Place swab back into the transport tube.

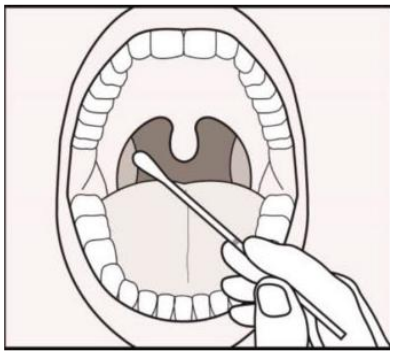
e. Collecting the NP swab.

- Ask the patients to attempt to clear the discharge by “blowing” his/her nose into nonscented tissue paper. (Allow one attempt.)
- Assist children whenever necessary.
- Do not try to clear the discharge with swabs, as this might be excessively traumatic.
- Insert swab into the nares.
- Insert flexible wire shaft swab through the nares parallel to the palate (not upwards) until resistance is encountered or the distance is equivalent to that from the ear to the nostril of the patient indicating contact with the nasopharynx.
- Gently, rub and roll the swab. Leave the swab in place for several seconds to absorb secretions before removing.

f. Collecting the OP swab.

- Identify participant and explain the procedure.

- Put on personal protective equipment.
- Check clearness, color, expiration date and absence of leakage of the collection tube.
- Tilt participant's head back and depress the tongue.
- Note: For young children: have child sit on the parent's lap facing forward with the child's back against the parent's chest. The parent should wrap one arm around the child in a manner that will restrain the child's body and arms. Ask the parent to tilt the child's head-backwards.
- Firmly swab the tonsillar area on both sides and the pharyngeal arches and leave in place for 5-10 seconds to absorb secretions, then withdraw the swab.
- Remove the cap from the VTM tube and insert the swab into the tube.
- Break the swab shaft, replace the cap and close the collection tube tightly. Make sure the swab shaft is short enough to permit complete tightening of the cap. Insert swab into the posterior pharynx and tonsillar areas.
- Rub swab over both tonsillar pillars and posterior oropharynx and avoid touching the tongue, teeth, and gums.
- For suspected diphtheria, swab behind the pseudo membrane.



g. Specimen handling.

- For virus : Place N, NP and OP swabs immediately into a sterile cryotube containing 1 ml of viral transport media without antibiotics. Both swabs can be 2 placed in the same cryotube, if desired. Aseptically, cut or break applicator sticks off near the tip to permit tightening of the cap.
- For virus : If specimens will be examined within 48 hours after collection keep specimen at 4ºC and ship on wet ice or refrigerant gel-packs, otherwise store frozen at ≤-70ºC and ship on dry ice. Avoid freezing and thawing specimens. Viability of some pathogens from specimens that were frozen and then thawed is greatly diminished and may result in false-negative test results
- For bacteria : Place swab immediately in Bacterial transport media : Amies transport media
- For bacteria : if specimens examined within 48 hours after collection, keep specimens in room temperature.
- Label the vial with the patient's name, ID number, specimen type, and date collected.

2. Nasopharyngeal wash/aspirate.

This specimen is commonly collected in children

a. Optimal timing.

Specimens should be collected within 3 days of symptom onset and not later than 7 days from all patients meeting the case definition identified during the outbreak or case finding, ideally prior to the initiation of antimicrobial chemoprophylaxis or therapy.

b. Specimen collection.

- Have the patient sit with head tilted slightly backward. Instill 1 ml-1.5 ml of non-bacteriostatic saline (pH 7.0) into one nostril. Flush a plastic catheter or tubing with 2 ml-3 ml of saline.
- Insert the tubing into the nostril parallel to the palate (not upwards). Aspirate nasopharyngeal secretions.
- If permitted, repeat this procedure for the other nostril.

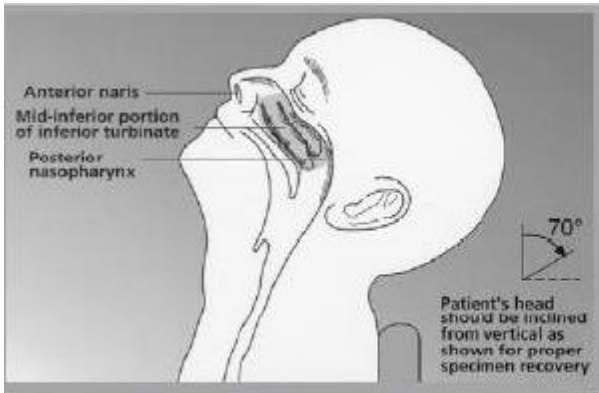


Figure 1: Proper Position for Sampling

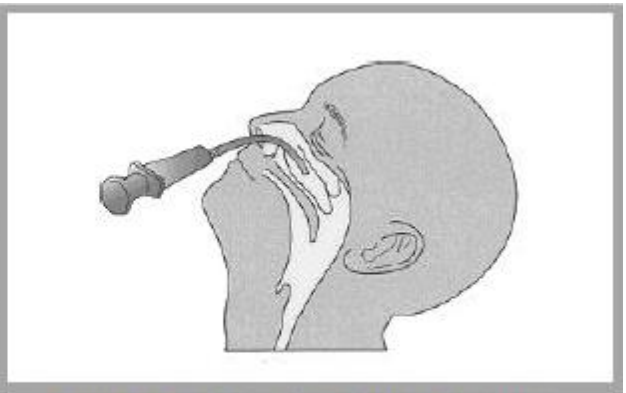


Figure 2: Syringe (or bulb) for collecting NP aspirate or washings

c. Specimen handling.

- Collect the specimens in sterile vials.
- Label each specimen container with the patients name, ID number, specimen type, and the date collected.
- If specimens will be examined within 48 hours after collection, keep specimen at 4ºC and ship on wet ice or refrigerant gel-packs, otherwise store frozen at ≤-70ºC and ship on dry ice.
- Avoid freezing and thawing specimens. Viability of some pathogens (e.g. respiratory syncytial virus) from specimens that are frozen and then thawed is greatly diminished and may result in false-negative test results.

B. Collection of Lower Respiratory Tract Specimens

1. Sputum, induced sputum, tracheal aspirate, bronchoalveolar lavage (BAL) fluid, pleural fluid

   Due to the increased technical skill and equipment needs, collection of specimens other than sputum from the lower respiratory tract may be limited to patients presenting with more severe disease, including persons admitted to the hospital and/or fatal cases.

a. Optimal timing.

   These specimens may be obtained at any time during the clinical course, but ideally prior to initiation of antimicrobial therapy.

b. Specimen types.

- Acceptable lower respiratory tract specimens include sputum, tracheal aspirate, BAL fluid, pleural fluid, or lung biopsy.
- Specimens with less chance for upper airway contamination (i.e., BAL fluid, pleural fluid, lung biopsy) are preferred.

c. Specimen collection.

i. BAL fluid, tracheal aspirate, pleural fluid Collect specimens in sterile containers.

- These specimens will be collected by a physician or other suitably qualified person by local practice.
- The lavage fluids will be collected into a sterile container.
- Label the specimen container with the participants ID number, date and time of the sample was collected.
- Transfer the sample to the study site laboratory.
- Aliquot 1.0 mL of sample into cryovials. If the laboratory cannot aliquot soon after receipt, store the sample in the refrigerator until ready to aliquot.
- Label each specimen container with the participants ID number, date, time and specimen type
- Store at -20^{o}C or below until shipment

ii. Sputum and induced sputum

- Note, a specimen may be obtained by sterile suction technique only by physician order.
- If possible, have the participant rinse mouth and gargle with water prior to sputum collection. Instruct the participant not to spit saliva or postnasal discharge into the container.
- A Gram stain smear result on sputum specimens will show epithelial cells. A sputum specimen containing >25 epithelial cells per low power

field has been contaminated with oropharyngeal secretions during collection, indicating a poor quality specimen for culture.
- Educate the patient about the difference between sputum and oral secretions.
- Have the patient rinse the mouth with water and then expectorate deep cough sputum directly into a sterile screw-cap collection cup or sterile dry container.

d. Specimen handling.

- Label the vial or container with the patient's name, ID number, specimen type, and date collected. Store fixed cells at room temperature.
- If unfixed specimens will be examined within 48 hours after collection, keep specimen at 4ºC and ship on wet ice or refrigerant gel-packs, otherwise store frozen at ≤-70ºC and ship on dry ice. Avoid freezing and thawing specimens. Viability of some pathogens from specimens that were frozen and then thawed is greatly diminished and may result in false-negative test results.

C. Collection of Blood Components

1. Acute and convalescent serum/plasma specimens.

If possible, acute and convalescent sera should be obtained from all patients identified during the outbreak. For most respiratory pathogens, both acute and convalescent sera must be collected to permit a definitive diagnosis. Antibody titers against suspected bacteria or viruses may be measured in sera and provide an important adjunct to or confirmation of PCR and culture results. However, these results are not timely enough to guide clinical care.

a. Optimal timing.

i. Acute. Acute serum/plasma specimens should be collected within one week of symptom onset as soon as possible.

ii. Convalescent. Convalescent specimens should be collected and submitted at day **after day 14th** after the acute specimen was collected.

b. Collecting the sera.

- For each serum specimen, collect 5 ml of whole blood into a serum separator tube (Red top or SST top).
- Centrifuge 3000 rpm for 15 minutes. Pipette serum using transfer pipette or clinipipette into cryo (NUNC) tube
- A minimum of 1 ml of whole blood is needed for testing of pediatric patients.
- Labeled cryo (NUNC) tube. Store at temperature - 70ºC or -80ºC.
- Ship with dry ice

c. Collecting the plasma & Buffy coat.

- For each plasma specimen, collect 2 x 3 ml EDTA tubes.
- Centrifuge 3000 rpm for 15 minutes.
- Pipette plasma using transfer pipette or clinipette.
- If aliquoting is performed, divide the sera into 0.5 ml aliquots in cryotube.
- After plasma separated from above process, transfer buffy coat using clinipipette yellow tip or transfer pipette ± 200 ul from each EDTA tube 3 ml into cryo (NUNC) tube.
- Label each vial with the patient's name, ID number, specimen type, and date collected.
- Store refrigerated at 4ºC or frozen (-70ºC), and ship on refrigerant gel packs or dry ice.

d. Collecting the PBMC

- For each PBMC specimen, collect 2 x 3 ml Heparin tubes or 1 CPT tubes
- Processing blood as soon as possible
- Label the tube with the patient's name, ID number, specimen type, and date collected.
- Store PBMC in liquid nitrogen

e. Collecting the paxgene

- Label the tube with the patient's name, ID number, specimen type, and date collected.
- Draw blood using a winged blood collection set
- The PAXgene tube must remain upright during collection.
- Full 2.5 ml of blood must be collected
- Invert tube 8-10 times after blood is collected
- Place tube in a wire rack.
- Store tube at -20ºC for 24 hours until frozen.
- After frozen, store the tube in the rack to freezer -80ºC

2. Whole blood for Culture.

This specimen may be limited to patients with more severe disease including persons admitted to the hospital.

a. Optimal timing.

Whole blood should be collected as soon as possible after illness onset and ideally before initiation of antimicrobial chemoprophylaxis or therapy. For fatal cases, postmortem whole blood should always be obtained at autopsy.

b. Collection.

Collect whole blood in bottles (culture media) ex: Bactec or BaTallert according to clinical laboratory guidelines.

c. Specimen handling.

Label the bottle with the patient's name, ID number, specimen type, and date collected.
Store and ship specimens in room temperature.

D. Urine

a. Optimal timing.

Urine may be collected within 7 days of symptom onset

b. Specimen collection.

- Random midstream urine will be collected if urine analysis is requested by the attending physician.
- Urine samples will be collected according to standard procedures. If standard procedures are not available then provide the participant with a sterile, plastic, preservative-free screw-top urine collection cup and instruct them to clean the labia or retract the foreskin prior to specimen collection.
- The participant should be asked to direct the first part of the urine void into the toilet, collect the middle part into the sterile cup and void the remaining urine into the toilet. Then the participant should screw the lid tightly onto the cup after collection.
- Collect 10-20 ml of mid stream urine in a container.
- Divide urine into 5 barcodes labeled cryo (NUNC) tube, each: 1000 uL. Store at temperature 70ºC or -80ºC.

c. Specimen handling.

- Label the container(s) with the patient's name, ID number, specimen type(s), and date collected.
- Store refrigerated at 4ºC and ship on dry ice or refrigerant gel packs.

E. Stool/Rectal Swab

a. Optimal timing.

Stool/Rectal Swab may be collected within 14 days of symptom onset from patients hospitalized as part of an disease outbreak (e.g. from SARS CoV suspect cases for RT-PCR).

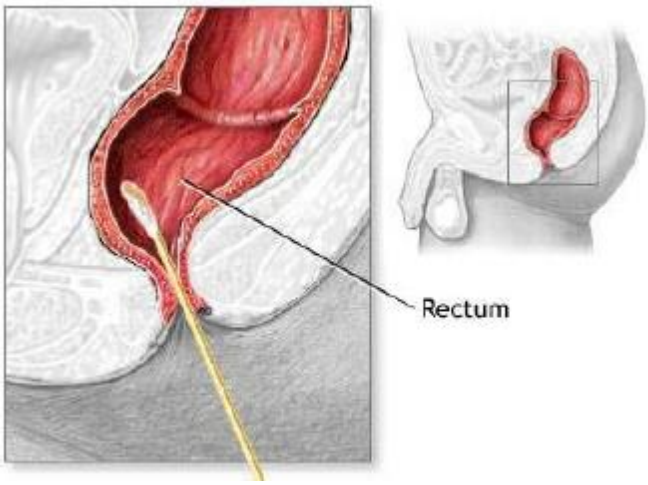
b. Stool Specimen collection.

- Collect 3 ml watery stool or 3 grams stool in a clean, dry, leak-proof container.
- Stool specimens should be collected into a clean, dry, leak-proof container.

- Label each specimen container with the participants ID number, date and time of the sample was collected.
- Transfer the sample to the study site laboratory.
- Take 3 grams of stool to 15 ml centrifuge tube. Dilute stool with PBS with ratio 1:1 (gr/volume solid or volume/volume watery stool) and centrifuge at 2000 rpm for 5 mins. Then aliquot 0.2 mL of the supernatant into 6 cryovials.
- Label each specimen vial with the participants ID number, date, time and specimen type which is classified by the color.
- Store at - 20 or below until shipment (See section

c. Rectal swab specimen collection.

- Identify participant and explain the procedure.
- Put on personal protective equipment.
- Check clearness, colour, expiration date and absence of leakage of the collection tube.
- Have participant lie on his/her back or side with upper legs and knees flexed towards the abdomen (crouching position).
- Moisten swab in normal saline or water.
- Carefully insert the swab through the anus in the participant's rectum (See Figure) and gently rotate a few times, leave in place for 5-10 seconds to absorb secretions, then withdraw swab carefully.
- Put the swab into the transport media tube 8. Label specimen transport tube with participants ID, date and time of sample collection. 9. Transfer the sample to the study site laboratory. 10. Affix the sample tube with the color sticker (see section 7.3). 11. Store at -20oC or below until shipment
- For bacterial examination, put the swab into the bacterial transport media (example: amies).
- For viral examination, put the swab into the VTM (Virus Transport Media) example: Hank's Solution



d. Specimen handling.
- Label the container(s) with the patient's name, ID number, specimen type(s), and date collected.
- If specimens will be examined within 48 hours after collection, they can be refrigerated at 4ºC; otherwise store frozen at -70ºC and ship on dry ice.

F. OTHER BODY FLUID (Cerebrospinal Fluid / CSF, Acites, Pus etc)

a. Optimal timing.

Specimens may be collected within 7 days of symptom onset

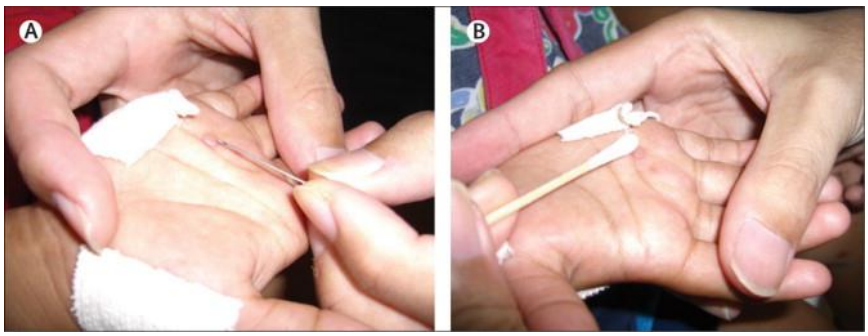
d. Specimen collection.

- CSF specimens will be collected according to the attending physician's decision. 2.
- The CSF fluid will be collected into a sterile container.
- Label the specimen container with the participants ID number, date and time of the sample was collected.
- Transfer the sample to the study site laboratory. * (CSF specimens should be transported to a microbiology laboratory as soon as possible. Specimens for culture should not be refrigerated or exposed to extreme cold, excessive heat, or sunlight. They should be transported at temperatures between 20°C and 35°C).
- Aliquot 1.0 mL of sample into cryovials.

e. Specimen handling.

- Label the container(s) with the patient's name, ID number, specimen type(s), and date collected.
- Store refrigerated at 4ºC or 20ºCand ship on dry ice or refrigerant gel packs.

G. OTHER SPECIMENS (SWAB VESICLE OR SKIN LESSION)



A. For virus : swabs immediately into a sterile cryotube containing 1 ml of viral transport media without antibiotics. Aseptically, cut or break applicator sticks off near the tip to permit tightening of the cap.
B. For virus : If specimens will be examined within 48 hours after collection keep specimen at 4ºC and ship on wet ice or refrigerant gel-packs, otherwise store frozen at ≤-70ºC and ship on dry ice. Avoid freezing and thawing specimens. Viability of some pathogens from specimens that were frozen and then thawed is greatly diminished and may result in false-negative test results
C. For bacteria : Place swab immediately in Bacterial transport media : Amies transport media
D. For bacteria : if specimens examined within 48 hours after collection, keep specimens in room temperature.
E. Label the vial with the patient's name, ID number, specimen type, and date collected.

15. Appendix 3. Implementing Arrangement on Infectious Diseases Research between US-NIH and Indonesia-NIHRD

IMPLEMENTING ARRANGEMENT
BETWEEN
THE NATIONAL INSTITUTES OF HEALTH OF THE DEPARTMENT OF HEALTH AND HUMAN SERVICES OF THE UNITED STATES OF AMERICA
AND
THE NATIONAL INSTITUTE OF HEALTH RESEARCH AND DEVELOPMENT OF THE MINISTRY OF HEALTH OF THE REPUBLIC OF INDONESIA
ON
INFECTIOUS DISEASE RESEARCH

The National Institutes of Health of the Department of Health and Human Services of the United States of America and the National Institute of Health Research and Development of the Ministry of Health of the Republic of Indonesia, hereinafter referred to as "the Parties",

Pursuant to the Agreement between the Government of the United States of America and the Government of the Republic of Indonesia on Scientific and Technological cooperation, signed at Jakarta on 29 March 2010, hereinafter the "S&T Agreement",

Based on their mutual and shared interests to continue to strengthen and to further develop cooperation in biomedical, clinical and public health research, and research capacity,

Have agreed as follows:

ARTICLE 1
OBJECTIVES

The objectives of this Implementing Arrangement are to provide a framework for conducting cooperation in infectious diseases research and to promote cooperation between the Parties for mutual benefit, public health and other peaceful purposes.

ARTICLE 2
AREAS OF COOPERATION

The Parties agree to cooperate in the following areas:

1. To conduct collaborative research on infectious disease priorities of significance to Indonesia;
2. To provide epidemiological and clinical data that are essential for improving and/ or developing clinical management and health policies;
3. To enhance research capacity and networking in infectious diseases in Indonesia;
4. To establish a repository of biological specimens in Indonesia for future study, such as for studies to determine the etiology of undiagnosed fever and/or its pathogenicity and its public health importance.

Initials: FSS

Page 1 of 4

ARTICLE 3
COMPONENT ENTITIES

1. Component entities of the Parties namely, the U.S. National Institute of Allergy and Infectious Diseases of the U.S. National Institutes of Health (NIAID/NIH), and the Indonesian National Institute of Health Research and Development of the Indonesia Ministry of Health (NIHRD/MoH) - will coordinate, oversee and undertake the objectives envisioned by this Implementing Arrangement.
2. NIAID and NIHRD agree to appoint the Indonesia Research Partnership on Infectious Diseases (INA-RESPOND) to undertake the implementation of cooperation envisioned by this Implementing Arrangement.

ARTICLE 4
IMPLEMENTATION

1. The Parties will conduct activities undertaken pursuant to this Arrangement in accordance with applicable laws, regulations and policies of the respective countries of the Parties and subject to the availability of personnel, resources, and appropriated funds.
2. Collaborative research activities will be undertaken under this Arrangement through the use of jointly developed non-binding plans, protocols, and other operational-level documentations, which shall be subject to review by the Parties.
3. Research activities under this Arrangement will, subject to availability of appropriated funds and other resources, be jointly funded, as mutually agreed.
4. For each subsequent research activity, a study protocol will be developed and approved by the Parties.
5. The specimens collected under the activities of this Arrangement shall be stored in a specimen repository in Indonesia.
6. The Parties may review or amend all or any part of operational level documentation related to the research, as mutually determined.

ARTICLES 5
INTELLECTUAL PROPERTY

The intellectual property of research results will be governed by the Protection of Intellectual Property (IPR) terms as provided under Article X, Protection of Intellectual Property, and Annex I, Intellectual Property Rights, of the S&T Agreement.

ARTICLE 6
MATERIAL TRANSFER AGREEMENTS

1. All activities under this Arrangement using research material originating from Indonesia shall to the fullest extent possible be conducted in Indonesia.

Initials: ____ / ____

2. Any transfer of research materials shall be carried out in accordance with Article VIII of the S&T Agreement, including in any Material Transfer Agreements to be concluded between the Parties in accordance with their respective applicable laws and regulations.

ARTICLE 7
GENETIC RESOURCES AND TRADITIONAL KNOWLEDGE

1. The collection, conservation and exchange of genetic resources and associated traditional knowledge under this Implementing Arrangement shall be in accordance with both Parties' applicable laws, regulations and procedures and subject to Article VI and Article X of the S&T Agreement.
2. If genetic resources or traditional knowledge are shared through mutually agreed research plans or protocols pursued under this Arrangement, sharing or transfer agreements will be concluded between the Parties in accordance with their respective applicable laws and regulations, and the provisions of the S&T Agreement and its Annex I.

ARTICLE 8
AMENDMENT

1. The Parties may review progress under this Arrangement by request in writing.
2. This Arrangement may be amended by mutual written agreement of the Parties.
3. Any such amendments shall enter into force on such date as may be decided mutually by the Parties.

ARTICLE 9
DURATION AND TERMINATION

1. This Arrangement shall enter into force on the date of the last signature of the Parties.
2. This Arrangement shall remain in force for a period of 3 (three) years and may be extended by mutual written consent of the Parties.
3. Either Party may terminate this Arrangement at any time by giving 6 (six) months prior written notice to the other Party.
4. Such termination shall not affect any project or program carried out under this Arrangement and not completed upon termination of this Arrangement.

Initials: FSC / [illegible]

IN **WITNESS WHEREOF,** the undersigned, being duly authorized by their respective Governments, have signed this Implementing Arrangement.

DONE in the English and Indonesian languages, both texts being equally authentic.

FOR THE NATIONAL INSTITUTES OF HEALTH OF THE DEPARTMENT OF HEALTH AND HUMAN SERVICES OF THE UNITED STATES OF AMERICA

Francis S. Collins, MD, PhD

Director of the National Institutes of Health of the Department of Health and Human Services of the United States of America

Place/Date: Bethesda, MD, USA 14 Dec 2016

FOR THE NATIONAL INSTITUTE OF HEALTH RESEARCH AND DEVELOPMENT OF THE MINISTRY OF HEALTH OF THE REPULBIC OF INDONESIA

Untung Suseno Sutarjo, MD, MPH

Secretary General of the Ministry of Health of the Republic of Indonesia

Place/Date: JAKARTA, 23 DEC 2016

16. Appendix 4. Extension of the Implementing Arrangement

MINISTRY OF HEALTH REPUBLIC OF INDONESIA
SECRETARIAT GENERAL
HR. Rasuna Said Street Block X-5 Kavling 4-9 Jakarta 12950
Phone (+6221) 5201590 *(Hunting)*

GERMAS

Your Ref. : KS.02.02/V/1341/2019 22 April 2019
Subject : Extension of Implementing Arrangement

Mr. Francis S. Collins, MD., Ph.D.
Director for National Institutes of Health
Bethesda, Maryland, United States

Dear Mr. Collins,

I would like to acknowledge the receipt of your letter dated 30 January 2019 regarding Implementing Arrangement between the National Institutes of Health of the Department of Health and Human Services of the United States of America and the National Institute of Health Research and Development of the Ministry of Health of the Republic of Indonesia on Infectious Diseases Research.

The Ministry of Health Republic of Indonesia welcomes the proposal of National Institutes of Health to extend the Arrangement. For the period of 2 (two) years, starts from 23 December 2019 until 23 December 2021.

Thank you for your attention and cooperation, and I look forward to further close collaboration between the National Institutes of Health of the Department of Health and Human Services of the United States of America and the National Institute of Health Research and Development of the Ministry of Health of the Republic of Indonesia.

Best Regards,

Oscar Primadi
Secretary General
Ministry of Health, Republic of Indonesia

Cc.
1. Minister of Health, Republic of Indonesia
2. National Institute of Health Research and Development, Ministry of Health, Republic of Indonesia

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

National Institutes of Health
Bethesda, MD 20892

January 30, 2019

Dr. Oscar Primadi, MPH
Secretary General, Ministry of Health
Kementerian Kesehatan Republik Indonesia

Dear Dr. Oscar Primadi,

The National Institutes of Health (NIH) refers to the Implementing Arrangement between the National Institutes of Health of the Department of Health and Human Services of the United States of America, and the National Institute of Health Research and Development of the Ministry of Health of the Republic of Indonesia on Infectious Disease Research, signed at Bethesda and Jakarta on December 14 and 23, 2016, respectively ("the Arrangement").

Article 9 of the Arrangement provides that the Arrangement "may be extended by mutual written consent of the Parties." NIH proposes that the Arrangement be extended for a five-year period with effect from December 23, 2019.

If the National Institute of Health Research and Development of the Ministry of Health of the Republic of Indonesia agrees with the proposal set forth above, NIH further proposes that this letter and the affirmative letter in reply from the National Institute of Health Research and Development of the Ministry of Health of the Republic of Indonesia shall constitute an agreement between the two agencies, which shall enter into force on the date of the letter in reply.

Sincerely,

Francis S. Collins, M.D., Ph.D.
Director, National Institutes of Health

17. Appendix 5 Molecular and serology tests at the INA-RESPOND Laboratory

Pathogen	Methods	Confirmation
Dengue virus	Molecular: real-time PCR(1) and nested PCR(2)	DENV RNA was detected
	Antigen detection (Focus Technology, US)	NS1 antigen was detected
	Serology assay: ELISA IgM and IgG (Focus Technology, US)	Sero-conversion in IgM and or IgG between acute and convalescent specimens; four-fold increase of IgG in the absence of IgM; detectable IgM, supported by IgG and clinical manifestations.
Salmonella typhi/ Salmonella paratyphi	Blood culture (Bactec or ViTek)	Identified by API
	Molecular: *S. typhi*(3), *S. paratyphi*(4)	*S. typhi/S. paratyphi* DNA was detected
	S. typhi antibodies by ELISA (MyBioSource, US) IgM and IgG	Sero-conversion or increasing of IgM and/or IgG antibodies titer. Detection of IgM in acute samples, supported by clinical manifestations.
Rickettsia typhi	Molecular: *Rickettsia spp.*(5), *R. typhi*(6)	*R. typhi* DNA was detected, if only *Rickettsia spp.* is detectable, it is supported by *R. typhi* IgM and IgG antibodies
	R. typhi ELISA IgM/IgG antibodies using ELISA (Fuller, US)	Sero-conversion or increasing titers of *R. typhi* IgM and IgG antibodies in convalescent specimens.
	Murine typhus IFA (Focus, US)	Increase in Fluorescein level in convalescent specimens, in line with ELISA results
Orientia tsutsugamuchi	Molecular: *Orientia tsutsugamuchi*(5)	*O. tsutsugamuchi* DNA was detected
	Scrub typhus ELISA IgM and IgG antibodies (InBios, US)	Sero-conversion or increasing titers of IgM and/or IgG *O. tsutsugamuchi* antibodies in convalescent specimens
Leptospira	Micro agglutination test (MAT) in a few specimens	Four-fold increase of Leptospira antibodies to certain species, or a high titer (1/320) of antibodies in a single acute specimen
	Molecular: real time PCR(7)	Leptospira DNA was detected
	ELISA IgM leptospira (PanBio, Aus), IgG Leptospira (Serion, Germany)	Sero-conversion or increasing IgM and IgG titers in convalescent specimens
Chikungunya virus	Molecular: real time PCR(8)	Chikungunya RNA was detected
	ELISA IgM and IgG chikungunya antibodies (Euroimmune, Germany)	Sero-conversion or increasing titers of IgM and IgG in convalescent specimens
Malaria	Thick blood smear (microscopic) or Rapid Antibody test (SD Bioline, US)	Plasmodium was detected Antibody was detected
Mycobacterium tuberculosis	Acid fast bacilli smear (microscopic)	Acid fast bacilli was detected
Mycobacterium leprae	Acid fast bacilli smear (microscopic)	Acid fast bacilli was detected
Amoeba coli/ Amoeba histolytica	Microscopic examination	Amoeba was detected
Helminthiasis	Microscopic examination	Helmith eggs or spores were detected
Other parasites	Microscopic examination	A parasite was detected
Seoul virus	Molecular: conventional PCR(9)	Seoul virus RNA was detected
	ELISA IgM and IgG Hantavirus Antibodies (Focus diagnostics)	Sero-conversion or increasing titers of IgM and IgG Hantavirus anti bodies in convalescent specimens
Rubella virus	ELISA Rubella virus IgM and IgG antibodies (Serion, Germany)	Sero-conversion or increasing titers of IgM and IgG antibodies in convalescent specimens
Influenza virus	Molecular: multiplex real-time PCR(10)	Influenza RNA virus was detected
	ELISA Influenza A and B virus IgM and IgG antibodies (Serion, Germany)	Two fold increase of IgM and/or IgG influenza A or Influenza B antibodies in convalescent specimens
Respiratory syncitial virus	Molecular: multiplex real-time PCR(10)	RSV RNA was detected
	ELISA RSV IgM and IgG antibodies (Serion, Germany)	Sero-conversion or increasing of IgM or IgG RSV antibodies in convalescent specimens
Para- influenza viruses	Melecular: multiplex real-time PCR(10)	Para influenza virus RNA was detected
Adenovirus	Melecular: multiplex real-time PCR(10)	Adenovirus RNA was detected
Cor OC43	Melecular: multiplex real-time PCR(10)	CorOC43 virus RNA was detected
Parechovirus	Melecular: multiplex real-time PCR(10)	Parechovirus RNA was detected
Bocavirus	Melecular: multiplex real-time PCR(10)	Bocavirus RNA was detected

Rhinovirus	Melecular: multiplex real-time PCR(10)	Rhinovirus RNA was detected
Metapneumovirus	Melecular: multiplex real-time PCR(10)	Metapneumovirus RNA was detected
Measles virus	Molecular: conventional(11)	Measles virus RNA was detected
	ELISA measles virus IgM and IgG antibodies (Serion, Germany)	Sero-conversion or increase titers of IgM and/or IgG antibodies in convalescent specimens
HHV-6	Conventional PCR(12)	HHV-6 virus DNA was detected
	Real-time PCR(13)	>1,000 copies/ul
Enterovirus	Real-time PCR(14)	Enterovirus RNA was detected
Flavivirus	Conventional PCR(15)	Flavivirus RNA was detected
Zikavirus	Real-time PCR(16)	Zikavirus RNA was detected
Rotavirus	Real-time PCR(17)	Rotavirus RNA was detected
Norovirus	Real-time PCR(18)	Norovirus RNA was detected
Adenovirus (ent)	Real-time PCR(17)	Adenovirus RNA was detected
Astrovirus	Real-time PCR(18)	Astrovirus RNA was detected
Chlamydia pneumonia	Real-time PCR(19)	*C. pneumonia* DNA was detected
Chlamydia psitacci	Real-time PCR(20)	*C. pistacci* DNA was detected
Streptococcus pneumonia	Real-time PCR(21)	*S. pneumoniae* DNA was detected
Haemophilus influenza	Real-time PCR(21)	*H. influenza* DNA was detected
Bordetella pertussis	Real-time PCR(22)	*B. pertussis* DNA was detected
Legionella pneumoniae	Real-time PCR(23)	*L. pneumoniae* DNA was detected
Mycoplasma pneumoniae	Real-time PCR(24)	*M. pneumoniae* DNA was detected
Staphylococcus aureus	Real-time PCR[25]	*S. aureus* DNA was detected
Klebsiella pneumoniae	Real-time PCR[25]	*K. pneumoniae* DNA was detected
16S r RNA	Real-time PCR(7)	Bacterial DNA was detected
HIV	Real-time PCR[26]	HIV RNA was detected, HIV antibody was negative,
	Rapid Test SD®, Oncoprobe® ELISA 4th generation (Biorad®)	4th generation ELISA was positive

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Annex 1. In Response to SARS-CoV-2 Pandemic (ORCHID-COVID-19 Study)

This document outlines the procedures to identify and characterize Corona Virus Disease 2019 (COVID-19) in the INA-ORCHID study.

Background

Fifteen years after the Avian Influenza epidemic, Indonesia was recently hit by another respiratory outbreak, COVID-19, caused by the novel SARS-CoV-2. This virus belongs to *Coronaviridae* family, genus betacoronavirus, together with SARS-CoV and MERS-CoV. SARS-CoV-2 was first reported on 31 December 2020 in Wuhan, China, and then it rapidly spread globally to infect more than 10 million people in more than 200 countries by 15 July 2020. SARS-CoV-2 has infected more than 80,000 people in all provinces in Indonesia,and has caused approximately 5% death. In response to this pandemic, a scientific research is necessary to systematically collect epidemiological and clinical data, along with biological specimens. Data and specimens obtained from this study are very important for identifying the best diagnostics, treatments, and prevention strategies in order to control the disease.

Objectives

Consistent with the objectives in the main protocol, focus on COVID-19.

Primary Objective:

To identify COVID-19 and other respiratory infectious disease cases from hospitalized suspected COVID-19 patients.

Secondary Objectives:

- To describe the disease course and case management of COVID-19
- To assess the accuracy of diagnostic tests of COVID-19
- To better understand the pathogenesis of COVID-19
- To assess treatments and short-term outcomes of COVID-19
- To generate epidemiologic data to inform ongoing and future disease control and prevention efforts of COVID-19

Study Benefit

Consistent with the objectives in the main protocol, focus on COVID-19.

- Provide a better understanding of COVID-19, its epidemiology and clinical characteristics in Indonesia.
- Generate data to support evidence-based recommendations to health authorities for COVID-19 disease diagnostics, treatment, and prevention.

- Improve the INA-RESPOND Network's capacity for conducting infectious disease research during dynamic outbreak scenarios, and it will strengthen the specialization of the Reference Laboratory to identify SARS-CoV-2 and other respiratory pathogens.

Sample Size and Study Duration

As a part of the INA-ORCHID study that will enrol 4000 subjects over 5 years, this ORCHID-COVID-19 study will enrol 500 suspected COVID-19 subjects from 5 hospitals over 1 year.

Study Method

This study will enrol suspected COVID-19 subjects to the prospective arm in outbreak situation of the INA-ORCHID study. It is an observational study with exploratory design. There will be no intervention that will affect standard of care or clinical outcome.

Study visit and Procedure:

Consistent with the main protocol, subjects will be seen during enrolment (visit 1), 7-14 days later (visit 2), and if necessary, one additional visit after visit 2 without specific time frame. Data and specimens collected also refer to the main protocol.

Inclusion criteria (consistent with the main protocol, focus on COVID-19):

- Adult or child of any age undergoing a current episode of illness that is presumed COVID-19

Exclusion criteria: none (consistent with the main protocol).

Study Flow:

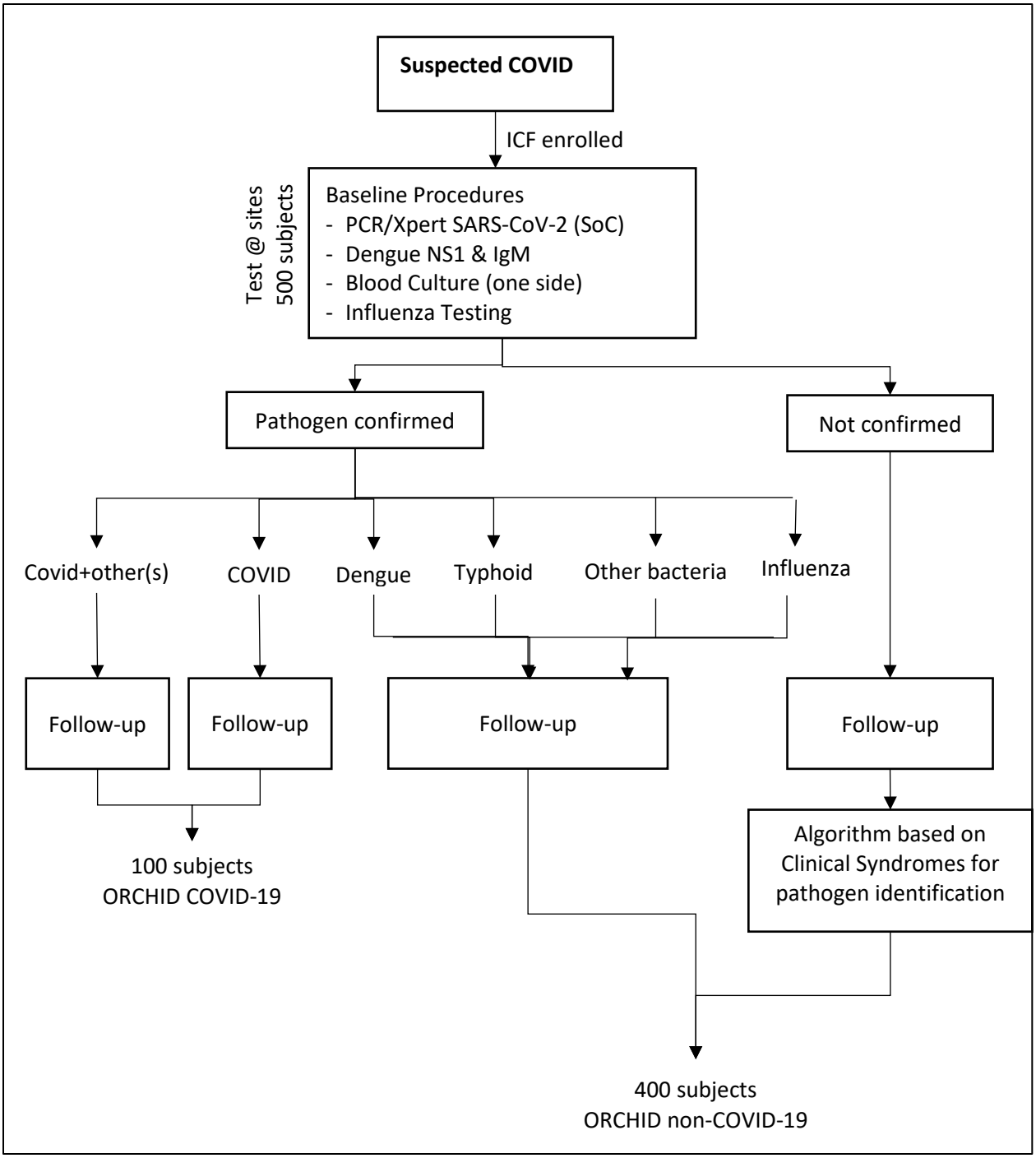
Of the 500 suspected COVID-19 patients who sign the consent form and are enrolled in the study, demographic and clinical data, clinical specimens are collected following INA-ORCHID protocol. COVID-19 RT-PCR is the hospital standard of care. As PCR results are usually available 24-72 hours later, other tests (dengue using NS1/IgM&IgG RDT, influenza virus using RDT, S typhi and paratyphi and other bacteria using blood culture) should be performed. Although confirmed dengue diagnosis even by positive NS1 will not exclude COVID-19, early dengue diagnosis will be very useful for patients, clinicians and hospital management. Blood culture during enrolment is recommended as it is the gold standard for S typhi and S paratyphi infections and should use blood before antibiotics are given to the patients. This blood culture may also identify other bacteria circulating in the blood. By conducting these tests, we are able to confirm COVID-19, dengue, influenza, *S typhi*, *S parathyphi*, other bacteria, and co-infections among them.

We expect 100 COVID-19 cases will be identified; however, the majority of cases may remain undiagnosed. For these cases, testing will be conducted at the reference lab based on clinical syndromes 1) COVID-19 that may be missed (viral shedding has passed, diagnosis will be based on serology). 2) dengue that may be missed (NS1 is often negative in secondary infection, diagnostic tests will use ELISA in paired sera and/or RT-PCR, 3) Salmonellas may be missed from blood culture and the only feasible diagnosis is using tubex test in paired sera. Sputum from pneumonia patients will be tested for virus and bacteria pneumonia panel. For testing other pathogens, the algorithm will be based on clinical syndromes and will be discussed with INA-RESPOND core and lab team and the sites.

All these 500 patients will follow INA-ORCHID study procedures during visit 1,2, and if necessary, visit 3.

Specimens from confirmed COVID-19 cases will be tested to understand the kinetics of the virus, IgM and IgG antibodies over-time, and to explore if there is certain people are more susceptible to contract severe disease. Data from COVID-19 cases can be used to better understand the epidemiology, disease progress and treatment outcomes. All the tests will be conducted at the reference lab.

The diagram of this study procedure is below.



Study Diagram for ORCHID-COVID-19 Study

Informed Consent Form for Pediatrics and Assent
Part I: Information Sheet

Title of study:	INA-RESPOND Observational Research on Infectious Disease Outbreaks and Difficult Cases of Unidentified Etiology in Indonesia
Protocol number:	INA107
Protocol PI:	Dr. Muhammad Karyana, MPH Gedung 3 Lantai 1 Badan Litbangkes Jl. Percetakan Negara No. 29 Jakarta, Indonesia - 10560 mkaryana@gmail.com
Site Number:	
Site PI:	
Participant's Name:	
Participant's ID:	

I am [*insert name of Site Investigator*], working for [*indicate Site name*] of the Indonesia Reseach Partnership on Infectious Diseases (INA-RESPOND). The INA-RESPOND is a research collaboration on infectious diseases between the National Institute of Health Research and Development, Ministry of Health of Indonesia and the National Institute of Allergy and Infectious Diseases, National Institutes of Health of the United States of America. We are doing research on [*indicate name of disease*], which is affecting a lot people in Indonesia. I am going to give you information and invite your child to be part of the study we are conducting. Before you decide whether your child will participate or not, you can talk to a friend, a family member or anyone else you feel comfortable with. We will do our best to facilitate the communication.

If I use some words that you do not understand, please ask me to stop and I will take time to explain. If you have questions later, you can ask them of me or [*indicate all research staff with whom participant will be in contact, e.g. study nurse, study physicians, etc*].

This Informed Consent Form has two parts:
- Information Sheet (to share information about the study with you)
- Consent Form (for signatures if you agree to take part)

Why is this research being done?
Your child are being asked to take part in this research because your child have been clinically diagnosed with [*indicate name of disease*] *OR* because we suspect your child have [*indicate name of disease*] *OR* because your child have been in contact with someone who has [*indicate name of disease*]. This research aims to understand the scope of pathogens (agent or organism that causes disease) responsible for outbreaks and difficult clinical cases in Indonesia, and to characterize the clinical course of the diseases to better inform diagnostics, treatments and prevention strategies.

What is the study about?
This study is about identifying the causative agents and describe the clinical conditions or characteristics of presumptive infections. It will involve data collection on demographics, medical history and clinical examination, and blood samples collection.

Is study participation mandatory?

Participation in research is entirely voluntary. It is your choice whether to participate or not. Whatever your decision, you will still access all health care services at your local clinic or hospital. If you decide to participate, you will be asked to sign the consent form at the end of this document to show that you agree. You can decide to participate now and change your mind later during the study. This will have no negative consequence for you or your child health.

How many people will be in this study?

The study is being conducted in Indonesia, particularly in 19 hospitals member of the INA-RESPOND Network *(RSUPN Dr. Cipto Mangunkusumo, RS Persahabatan, and RSPI Prof. Dr. Sulianti Saroso, RS St. Carolus, Jakarta; RSUD Kab. Tangerang, Banten; RSUP Dr. Hasan Sadikin, Bandung; RSUP Dr. Sardjito, Yogyakarta; RSUP Dr. Kariadi, Semarang; RSUD Dr. Soetomo, Surabaya; RSUP Dr. Wahidin Sudirohusodo, Makassar; RSUP Sanglah, Denpasar; RSUP Adam Malik, Medan; RS Budi Kemuliaan, Batam; RSUD Zainoel Abidin, Banda Aceh; RSUD Ansari Saleh, Banjarmasin; RSUD Abdul Wahab Sjahranie, Samarinda; RSUD Soedarso, Pontianak; RSUD TC Hilers, Sikka; RSUD Abepura, Jayapura)* for five years from 2020 to 2025. We plan to include up to 5,000 participants. We are inviting all adults *OR* all children with [*indicate name of disease*] to participate in the study.

What will happen if you decide your child to participate in this study?

If you agree that your child to be part of the study, your child will be asked to complete the study visits twice, at enrolment and baseline visit (day 0) and follow up visit (day 7-14) to conduct data and blood sample collection.

Screening

We will evaluate your child eligibility to take part in this study. The screening procedures will take up to 30 minutes.

Your child may be enrolled in this study if your child meets all the following criteria:

1. Child of any age hospitalized with a current episode of illness with a presumed infectious disease of unidentified etiology
2. Your child tested negative for Dengue virus infection by an antigen-based and antibody-based diagnostic test (i.e. NS1 antigen test and Dengue-specific IgM test)
3. Your child tested negative for Salmonella Typhi infection by Standard of Care testing (i.e. blood culture, Widal test, or Tubex rapid test)
4. You are able to provide a documented informed consent
5. You agree to the collection and storage of specimens of your child for laboratory testing and/or future research (you may decline storage of specimens for future research)

However, if your Site PI advised your child not to take part in this study to protect your child safety and wellbeing, your child may not be enrolled in this study.

Enrolment and Baseline Visit (Day 0)

After your child are enrolled in this study, we will collect your child baseline information. This procedure may take up to 30 minutes to 2 hours, your child will have the following done:

- We will ask you some questions about your general information, such as age, gender, residence and occupation. We will also ask you some questions about your child medical history, such as your child travel history, contact history to suspected human cases, insect or animal exposure, vaccination history, and medication use prior to enrolment.
- We will check your child height and weight, blood pressure, heart and respiratory rate, body temperature, and current signs and symptoms. We will also collect information on other diseases or conditions, results on laboratory and imaging tests done by your physicians, treatment and clinical outcome at this visit.
- About 0.5-1 tablespoon (5-15 mL) of your child blood will be drawn through the vein in your child forearm. We will also collect other non-invasive (not breaking, cutting, or entering the skin) samples such as sputum, urine, stool, nasopharyngeal swab, etc. if clinically indicated. Samples collected by your child physicians can be included if leftover specimen is shared.
- Based on your child's weight, the amount of blood drawn in one take will be adjusted according to the table below:

Your child's body weight (Kilograms)	Maximum blood volume per one take
4.5 – 6.8	5 ml
7.3 – 18.2	10 ml
>18.2	15 ml

- Routine hematology, blood chemistry, liver and renal function tests will be done to the collected blood samples. The remaining blood samples and other available samples will be processed for pathogen identification tests at INA-RESPOND Reference Laboratory.
- The remaining blood samples and other available samples will be processed and stored for future research (you may decline storage of specimens of your child for future research).

Follow Up Visit (Day 7-14)

Approximately 1-2 weeks after baseline evaluation, the study staff will contact you and continue with the study follow up. During which, your child will have the following done for up to 30 minutes to 2 hours:

- We will check your child height (if previously not done) and weight, blood pressure, heart and respiratory rate, body temperature, and current signs and symptoms. We will also collect information on other diseases or conditions, results on laboratory and imaging tests done by your physicians, treatment and clinical outcome at this visit.
- About 0.5-1 tablespoon (5-15 mL) of your blood will be drawn trough the vein in your child forearm. We will also collect other non-invasive (not breaking, cutting, or entering the skin) samples such as sputum, urine, stool,

nasopharyngeal swab, etc. if clinically indicated. Samples collected by your child physicians can be included if leftover specimen is shared.

- Based on your child's weight, the amount of blood drawn in one take will be adjusted according to the table below:

Your child's body weight (Kilograms)	Maximum blood volume per one take
4.5 – 6.8	5 ml
7.3 – 18.2	10 ml
>18.2	15 ml

- The blood samples and other available samples will be processed for pathogen identification tests at INA-RESPOND Reference Laboratory.
- The remaining blood samples and other available samples will be processed and stored for future research (you may decline storage of specimens of your child for future research).

Additional Study Visit (Beyond Day 14 up to one month)

If your child current episode of illness is deemed complex, where convalescent specimens (specimen that taken in recovering phase) are needed to identify etiology or where long-term sequelae are observed or anticipated, it is possible that additional follow up visit is conducted. Your child will have the following done for up to 30 minutes to 2 hours:

- We will check your child height (if previously not done) and weight, blood pressure, heart and respiratory rate, body temperature, and current signs and symptoms. We will also collect information on other diseases or conditions, results on laboratory and imaging tests done by your child physicians, treatment and clinical outcome at this visit.
- About 0.5-1 tablespoon (5-15 mL) of your child blood will be drawn through the vein in your child forearm. We will also collect other non-invasive (not breaking, cutting, or entering the skin) samples such as sputum, urine, stool, nasopharyngeal swab, etc. if clinically indicated. Samples collected by your child physicians can be included if leftover specimen is shared.
- Based on your child's weight, the amount of blood drawn in one take will be adjusted according to the table below:

Your child's body weight (Kilograms)	Maximum blood volume per one take
4.5 – 6.8	5 ml
7.3 – 18.2	10 ml
>18.2	15 ml

- The blood samples and other available samples will be processed for pathogen identification tests at INA-RESPOND Reference Laboratory.
- The remaining blood samples and other available samples will be processed and stored for future research (you may decline storage of specimens of your child for future research).

Your child involvement in the study will last for up to 2 weeks to 1 month, unless there are situations or circumstances that may cause your child participation in this study to be dropped early.

What are the risks and possible discomforts of being in this study?
There is an anticipated risks and discomforts associated with blood draw. These include slight pain and redness or bruising at the site where the blood is drawn and in rare cases, fainting. Bruising may be alleviated by a warm compress. There is a very small chance the site where the blood is drawn may become infected. This is unlikely since the person drawing the blood will clean the site with alcohol before blood is taken and use a sterile needle and blood drawing material.

What Happens If your Child Injured?
We will provide immediate medical care for study-related injuries e.g. an infection where blood has been taken. The study cannot pay for long-term disability that may have resulted from the participant's illness.

What are the possible benefits of being in this study?
Your child will not directly benefit from being in this study, except that if your child is in the study, your child will have closer medical follow-up than if you are not. Others in the future may benefit from knowledge gained during this research, as the study results may guide the future treatment *OR* diagnosis *OR* prevention of [*indicate name of disease*].

What are your responsibilities if your child participates?
If you agree that your child to participate in the study, we expect you and your child to comply with the study visit schedule and procedure as previously described. You may decide at any time that you or your child do not want to take part in the study anymore. If you do so, we may ask your child to come for a final medical visit to check that everything is alright.

Will you be paid to take part in this study?
You and your child will not be paid to take part in this study, but we will reimburse you for your time and travel to and from the clinic for your child study visits for up to Rp 150,000.00 per visit. Participating in the study will not incur any additional cost for you and your child. **However, you will still have to pay for all the treatment you received as part of the hospital's medical treatment**

What will happen to the samples collected during the study?
Samples collected during the study will be sent to INA-RESPOND Reference Laboratory for storage and analysis. If you agree, the stored samples may be used for future research on [*indicate name of disease*]. If we incidentally discover that your child has a severe, un-diagnosed disease we will inform you through your child physicians and make sure you have access to appropriate health care.

How will we protect confidentiality?
We will not share you and your child identity or that of any other study participant outside of the clinic. The only people who will know that your child is in the study are

members of the study team. No information about you and your child or provided by you and your child during the study, will be disclosed to others, except under the circumstances described below.

Your child name will not be mentioned on any sample, nor on the data collected during the study. Your child will be given a unique number, which will be used to identify the samples and data collected. If the results of this study get published in a scientific journal, your child name will not appear on the publication. All members of the study team commit to protect the confidentiality of the information you and your child provide. The members of the Ethics Committee, auditors, members of the drug regulatory authorities and the sponsor's representatives may conduct assessments of the study and verify it is conducted according to best research practices. In doing so they may have to access your child personal information, however, all these people have to respect the confidentiality, and your personal information will not be revealed publicly.

In addition, the Ministry of Health or designee may request access to your child personal information to prevent the further spread of [indicate name of disease] in your community.

A description of this study will be available on www.ina-registry.org and *www.ClinicalTrials.gov* .These Web sites will not include information that can identify your child. At most, the Web sites will include a summary of the results. You can search this Web sites at any time.

Will you and your child be informed of study findings?

The knowledge that we gain from doing this research will be shared with you and your child through community meetings or through your child physicians. Likewise, during the course of the study, you and your child will be informed of any significant new findings, such as changes in the risks or benefits resulting from participation in the study or new alternatives to participation, that might cause you or your child to change your mind about continuing in the study.

What should you do if you or your child want to stop taking part in the study?

You and your child can stop being in the study at any time, and without providing any justification for this decision. If you or your child decide to withdraw from the study, it will not affect the quality of your child care, and your child will still receive treatment for [*indicate name of disease*], according to the standard of care in use in [indicate name of study site]. Any information collected up to the point of your child withdrawal cannot be removed from the study. This includes any sample collected up until the date of withdrawal, which will be kept and analyzed. If you or your child decide to stop participating, please inform your study physicians or nurse.

What situations or circumstances that may cause your child participation in this study to be dropped early?

Your child involvement in the study will last for up to 2 weeks to 1 month, unless there are situations or circumstances that may cause your child participation in this study to be dropped early due to meet with below criteria:

- Your child specimen has been identified for the pathogens based on the specimen analysis
- Your child has discharged from hospital after Visit 2

- Your child has discharged from hospital and then completed Visit 2 and not require for additional visit
- Your child decides to withdraw from study participation
- You cannot be contacted and lost to follow-up or moves away from the study area
- Participant dies
- Your child was inadvertently enrolled such as not meeting the eligibility criteria
- Investigator determines that further participation would be detrimental to your child health or well-being
- The study is stopped for other administrative reasons

<u>If you or your child have questions or concerns about this study, whom can you call?</u>
If you have questions, concerns, or believe your child may have developed an injury related to this study, contact [*indicate Principal Investigator name*] at [*give PI direct phone number*].

This study protocol has been reviewed and approved by [*indicate name of IRB*], which is a committee whose task it is to make sure that study participants are protected from harm. If you wish to find out more about the *Institutional Review Board* (IRB), contact [*name and phone number*].

Informed Consent Form for Pediatrics
Part II: Parental Consent Form

INA-RESPOND Observational Research on Infectious Disease Outbreaks and Difficult Cases of Unidentified Etiology in Indonesia

- I have read the study information sheet, or the information sheet has been read to me. I have had the opportunity to ask questions about it and any questions I have asked has been answered to my satisfaction. I have been explained that I may withdraw from this study at any time.
- I freely and voluntarily choose my child to participate in this study. I will be given a copy of this information sheet and signed consent form to keep for my reference.

I agree to the storing of my child blood for future research.
☐ YES
☐ NO

Participant/Child Name:	_____	Date of birth:	___/___/____ (dd/mm/yy)
Parental relationship or legal custodianship with the child:	_____	Date of Consent:	___/___/____ (dd/mm/yy)
		Time of Consent:	_____
Name of Parent/Legal Guardian:	_____	Signature*:	_____

Name of the Investigator:	_____	Signature:	_____
Date of Consent:	___/___/___ (dd/mm/yy)	Time of Consent:	_____

Name of Witness:	_____	Signature:	_____
Date of Consent:	___/___/___ (dd/mm/yy)	Time of Consent:	_____

*a thumb print can be used if the person cannot write

Informed Consent Form for Pediatrics
Part II: Assent Consent Form

INA-RESPOND Observational Research on Infectious Disease Outbreaks and Difficult Cases of Unidentified Etiology in Indonesia

- I have read the study information sheet, or this information sheet has been read to me. I have had the opportunity to ask questions about it and any questions I have asked to have been answered to my satisfaction. I have been explained that I may withdraw from this study at any time.
- I freely and voluntarily choose to participate in this study. I will be given a copy of this information sheet and signed consent form to keep for my reference.

I agree to the storing of my blood for future research.
☐ YES
☐ NO

Participant Name:	_____	Date of birth:	___/___/____ (dd/mm/yy)
Signature*:	_____	Age:	_____
Date of Consent:	___/___/____ (dd/mm/yy)	Time of Consent:	_____
Parental relationship or legal custodianship with the child:	_____	Date of Consent:	___/___/____ (dd/mm/yy)
		Time of Consent:	_____
Name of Parent/Legal Guardian:	_____	Signature*:	_____

Name of the Investigator:	_____	Signature:	_____
Date of Consent:	___/___/___ (dd/mm/yy)	Time of Consent:	_____

Name of Witness:	_____	Signature:	_____
Date of Consent:	___/___/___ (dd/mm/yy)	Time of Consent:	_____

*a thumb print or mark “X” can be used if the person cannot write or illeterate

Informed Consent Form for Adults
Part I: Information Sheet

Title of study:	INA-RESPOND Observational Research on Infectious Disease Outbreaks and Difficult Cases of Unidentified Etiology in Indonesia
Protocol number:	INA107
Sponsors:	National Institute of Health Research and Development, Ministry of Health of Indonesia and the National Institute of Allergy and Infectious Diseases, National Institutes of Health of the United States of America
Site Number:	
Site PI Name:	
Site Address:	
Site PI Contact:	
Participant's Name:	
Participant's ID:	

I am [*insert name of Site Investigator or designee*], working for [*indicate Site name*] of the Indonesia Reseach Partnership on Infectious Diseases (INA-RESPOND). The INA-RESPOND is a research collaboration on infectious diseases between the National Institute of Health Research and Development, Ministry of Health of Indonesia and the National Institute of Allergy and Infectious Diseases, National Institutes of Health of the United States of America.

We are doing research on [*indicate name of disease*], which is affecting a lot people in Indonesia. I am going to give you information and invite you to be part of the study we are conducting. Before you decide whether you will participate or not, you can talk to a friend, a family member or anyone else you feel comfortable with. We will do our best to facilitate the communication.

If I use some words that you do not understand, please ask me to stop and I will take time to explain. If you have questions later, you can ask them of me or [*indicate all research staff with whom participant will be in contact, e.g. study nurse, study physicians, research assistants, etc*].

This Informed Consent Form has two parts:
- Information Sheet (to share information about the study with you)
- Consent Form (for signatures if you agree to take part)

<u>Why is this research being done?</u>
You are being asked to take part in this research because you have been clinically diagnosed with [*indicate name of disease*] *OR* because we suspect you have [*indicate name of disease*] *OR* because you have been in contact with someone who has [*indicate name of disease*]. This research aims to understand the scope of pathogens (agent or organism that causes disease) responsible for outbreaks and difficult clinical

cases in Indonesia, and to characterize the clinical course of the diseases to better inform diagnostics, treatments and prevention strategies.

What is the study about?
This study is about identifying the causative agents and describe the clinical conditions or characteristics of presumptive infections. It will involve data collection on demographics, medical history and clinical examination, and blood samples collection.

Is study participation mandatory?
Your participation in this study is entirely voluntary. It is your choice whether to participate or not. Whatever your decision, you will still access all health care services at your local clinic or hospital. If you decide to participate, you will be asked to sign the consent form at the end of this document to show that you agree. You can decide to participate now and change your mind later during the study. This will have no negative consequence for you or your health.

How many people will be in this study?
The study is being conducted in Indonesia, particularly in 19 hospitals member of the INA-RESPOND Network *(RSUPN Dr. Cipto Mangunkusumo, RS Persahabatan, and RSPI Prof. Dr. Sulianti Saroso, RS St. Carolus, Jakarta; RSUD Kab. Tangerang, Banten; RSUP Dr. Hasan Sadikin, Bandung; RSUP Dr. Sardjito, Yogyakarta; RSUP Dr. Kariadi, Semarang; RSUD Dr. Soetomo, Surabaya; RSUP Dr. Wahidin Sudirohusodo, Makassar; RSUP Sanglah, Denpasar; RSUP Adam Malik, Medan; RS Budi Kemuliaan, Batam; RSUD Zainoel Abidin, Banda Aceh; RSUD Ansari Saleh, Banjarmasin; RSUD Abdul Wahab Sjahranie, Samarinda; RSUD Soedarso, Pontianak; RSUD TC Hilers, Sikka; RSUD Abepura, Jayapura)* for five years from 2020 to 2025. We plan to include up to 5,000 participants. We are inviting all adults *OR* all children with [*indicate name of disease*] to participate in the study.

What will happen if you decide to participate in this study?
If you agree to be part of the study, you will be asked to complete the study visits twice, at enrolment and baseline visit (day 0) and follow up visit (day 7-14) to conduct data and blood sample collection.

Screening

We will evaluate your eligibility to take part in this study. The screening procedures will take up to 30 minutes.

You may be enrolled in this study if you meet all the following criteria:

1. You are adult of any age hospitalized with a current episode of illness with a presumed infectious disease of unidentified etiology
2. You tested negative for Dengue virus infection by an antigen-based and antibody-based diagnostic test (i.e. NS1 antigen test and Dengue-specific IgM test)
3. You tested negative for Salmonella Typhi infection by Standard of Care testing (i.e. blood culture, Widal test, or Tubex rapid test)
4. You are able to provide a documented informed consent
5. You agree to the collection and storage of specimens for laboratory testing and/or future research (you may decline storage of specimens for future research)

However, if your Site PI advised you not to take part in this study to protect your safety and wellbeing, you may not be enrolled in this study.

Enrolment and Baseline Visit (Day 0)

After you are enrolled in this study, we will collect your baseline information. This procedure may take up to 30 minutes to 2 hours, you will have the following done:

- We will ask you some questions about your general information, such as age, gender, residence and occupation. We will also ask you some questions about your medical history, such as your travel history, contact history to suspected human cases, insect or animal exposure, vaccination history, and medication use prior to enrolment.
- We will check your height and weight, blood pressure, heart and respiratory rate, body temperature, and current signs and symptoms. We will also collect information on other diseases or conditions, results on laboratory and imaging tests done by your physicians, treatment and clinical outcome at this visit.
- About 0.5-1 tablespoon (5-15 mL) of your blood will be drawn through the vein in your forearm. We will also collect other non-invasive (not breaking, cutting, or entering the skin) samples such as sputum, urine, stool, nasopharyngeal swab, etc. if clinically indicated. Samples collected by your physicians can be included if leftover specimen is shared.
- Routine hematology, blood chemistry, liver and renal function tests will be done to the collected blood samples. The remaining blood samples and other available samples will be processed for pathogen identification tests at INA-RESPOND Reference Laboratory.
- The remaining blood samples and other available samples will be processed and stored for future research (participants may decline storage of specimens for future research).

Follow Up Visit (Day 7-14)

Approximately 1-2 weeks after baseline evaluation, the study staff will contact you and continue with the study follow up. During which, you will have the following done for up to 30 minutes to 2 hours:

- We will check your height (if previously not done) and weight, blood pressure, heart and respiratory rate, body temperature, and current signs and symptoms. We will also collect information on other diseases or conditions, results on laboratory and imaging tests done by your physicians, treatment and clinical outcome at this visit.
- About 0.5-1 tablespoon (5-15 mL) of your blood will be drawn trough the vein in your forearm. We will also collect other non-invasive (not breaking, cutting, or entering the skin) samples such as sputum, urine, stool, nasopharyngeal swab, etc. if clinically indicated. Samples collected by your physicians can be included if leftover specimen is shared.
- The blood samples and other available samples will be processed for pathogen identification tests at INA-RESPOND Reference Laboratory.

- The remaining blood samples and other available samples will be processed and stored for future research (participants may decline storage of specimens for future research).

Additional Study Visit (Beyond Day 14 up to one month)

If your current episode of illness is deemed complex, where convalescent specimens (specimen that taken in recovering phase) are needed to identify etiology or where long-term sequelae are observed or anticipated, it is possible that additional follow up visit is conducted. you will have the following done for up to 30 minutes to 2 hours:

- We will check your height (if previously not done) and weight, blood pressure, heart and respiratory rate, body temperature, and current signs and symptoms. We will also collect information on other diseases or conditions, results on laboratory and imaging tests done by your physicians, treatment and clinical outcome at this visit.
- About 0.5-1 tablespoon (5-15 mL) of your blood will be drawn through the vein in your forearm. We will also collect other non-invasive (not breaking, cutting, or entering the skin) samples such as sputum, urine, stool, nasopharyngeal swab, etc. if clinically indicated. Samples collected by your physicians can be included if leftover specimen is shared.
- The blood samples and other available samples will be processed for pathogen identification tests at INA-RESPOND Reference Laboratory.
- The remaining blood samples and other available samples will be processed and stored for future research (participants may decline storage of specimens for future research).

Your involvement in the study will last for up to 2 weeks to 1 month, unless there are situations or circumstances that may cause your participation in this study to be dropped early.

What are the risks and possible discomforts of being in this study?

There is an anticipated risks and discomforts associated with blood draw. These include slight pain and redness or bruising at the site where the blood is drawn and in rare cases, fainting. Bruising may be alleviated by a warm compress. There is a very small chance the site where the blood is drawn may become infected. This is unlikely since the person drawing the blood will clean the site with alcohol before blood is taken and use a sterile needle and blood drawing material.

What Happens If I Am Injured?

We will provide immediate medical care for study-related injuries e.g. an infection where blood has been taken. The study cannot pay for long-term disability that may have resulted from the participant's illness.

What are the possible benefits of being in this study?

You will not directly benefit from being in this study, except that if you are in the study, you will have closer medical follow-up than if you are not. Others in the future may benefit from knowledge gained during this research, as the study results may guide the future treatment *OR* diagnosis *OR* prevention of [*indicate name of disease*].

What are your responsibilities if you participate?
If you agree to participate in the study, we expect you to comply with the study visit schedule and procedure as previously described. You may decide at any time that you do not want to take part in the study anymore. If you do so, we may ask you to come for a final medical visit to check that everything is alright.

Will you be paid to take part in this study?
You will not be paid to take part in this study, but we will reimburse you for your time and travel to and from the clinic for your study visits for up to Rp 150,000.00 per visit. Participating in the study will not incur any additional cost for you. **However, you will still have to pay for all the treatment you received as part of the hospital's medical treatment.**

What will happen to the samples collected during the study?
Samples collected during the study will be sent to INA-RESPOND Reference Laboratory for storage and analysis. If you agree, the stored samples may be used for future research on [*indicate name of disease*]. If we incidentally discover that you have a severe, un-diagnosed disease we will inform you through your physicians and make sure you have access to appropriate health care.

How will we protect confidentiality?
We will not share your identity or that of any other study participant outside of the clinic. The only people who will know that you are in the study are members of the study team. No information about you, or provided by you during the study, will be disclosed to others, except under the circumstances described below.

Your name will not be mentioned on any sample, nor on the data collected during the study. You will be given a unique number, which will be used to identify the samples and data collected. If the results of this study get published in a scientific journal, your name will not appear on the publication. All members of the study team commit to protect the confidentiality of the information you provide. The members of the Ethics Committee, auditors, members of the drug regulatory authorities and the sponsor's representatives may conduct assessments of the study and verify it is conducted according to best research practices. In doing so they may have to access your personal information, however, all these people have to respect the confidentiality, and your personal information will not be revealed publicly.

In addition, the Ministry of Health or designee may request access to your personal information to prevent the further spread of [*indicate name of disease*] in your community.

A description of this study will be available on *www.ina-registry.org* and *www.ClinicalTrials.gov*. These Web sites will not include information that can identify you. At most, the Web sites will include a summary of the results. You can search this Web sites at any time.

Will you be informed of study findings?
The knowledge that we gain from doing this research will be shared with you through community meetings or through your physicians. Likewise, during the course of the study, you will be informed of any significant new findings, such as changes in the

risks or benefits resulting from participation in the study or new alternatives to participation, that might cause you to change your mind about continuing in the study.

What should you do if you want to stop taking part in the study?
You can stop being in the study at any time, and without providing any justification for this decision. If you decide to withdraw from the study, it will not affect the quality of your care, and you will still receive treatment for [*indicate name of disease*], according to the standard of care in use in [*indicate name of study site*]. Any information collected up to the point of your withdrawal cannot be removed from the study. This includes any sample collected up until the date of withdrawal, which will be kept and analyzed. If you decide to stop participating, please inform your study physicians or nurse.

What situations or circumstances that may cause your participation in this study to be dropped early?

Your involvement in the study will last for up to 2 weeks to 1 month, unless there are situations or circumstances that may cause your participation in this study to be dropped early due to meet with below criteria:

- Your specimen has been identified for the pathogens based on the specimen analysis
- You have discharged from hospital after Visit 2
- You have discharged from hospital and then completed Visit 2 and not require for additional visit
- You decide to withdraw from study participation
- You cannot be contacted and lost to follow-up or moves away from the study area
- Participant dies
- You were inadvertently enrolled such as not meeting the eligibility criteria
- Investigator determines that further participation would be detrimental to your health or well-being
- The study is stopped for other administrative reasons

If you have questions or concerns about this study, whom can you call?
If you have questions, concerns, or believe you may have developed an injury related to this study, contact [*indicate Principal Investigator name*] at [*give PI direct phone number*].

This study protocol has been reviewed and approved by [*indicate name of IRB*], which is a committee whose task it is to make sure that study participants are protected from harm. If you wish to find out more about the Institutional Review Board (IRB), contact [*name and phone number*].

Informed Consent Form for Adults
Part II: Consent Form

INA-RESPOND Observational Research on Infectious Disease Outbreaks and Difficult Cases of Unidentified Etiology in Indonesia

- I have read the study information sheet, or the information sheet has been read to me. I have had the opportunity to ask questions about it and any questions I have asked has been answered to my satisfaction. I have been explained that I may withdraw from this study at any time.
- I freely and voluntarily choose to participate in this study. I will be given a copy of this information sheet and signed consent form to keep for my reference.

I agree to the storing of my blood for future research. ☐ YES ☐ NO

Printed Name of Participant:	_____	Date of birth:	___/___/____ (dd/mm/yy)
Signature:		Date:	___/___/____ (dd/mm/yy)
	_____	Time of Consent:	_____

Printed Name of the Investigator:	_____	Signature:	_____
Date:	___/___/____ (dd/mm/yy)	Time of Consent:	_____

Printed Name of Witness:	_____	Signature:	_____
Date:	___/___/____ (dd/mm/yy)	Time of Consent:	_____

***COMPLETE THIS SECTION ONLY IF THE PARTICIPANT IS UNCONSCIOUS OR TOO ILL TO CONSENT*

Participant Name:	_____	Date of birth:	___/___/____ (dd/mm/yy)
Relationship with the Participant:	_____	Date of Consent:	___/___/____ (dd/mm/yy)
		Time of Consent:	_____
Name of Parent/ Spouse/ Legal Guardian:	_____	Signature*:	_____
Name of the Investigator:	_____	Signature:	_____
Date of Consent:	___/___/___ (dd/mm/yy)	Time of Consent:	_____
Name of Witness:	_____	Signature:	_____
Date of Consent:	___/___/___ (dd/mm/yy)	Time of Consent:	_____

**A thumbprint or mark "X" can be used if the person cannot write or illiterate*
*** In case of severely ill participants, informed consent will be **obtained by LAR** (Legally Authorized Representative) and at first opportunity of well episode, **the participant will be reconsented.***