CHANG GUNG MEMORIAL HOSPITAL

Manual of Operating Procedures: Chang Gung Memorial Hospital

Human Influenza Surveillance of Health Care Centers in the United States and Taiwan

Version 1.0

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List of Abbreviations

AE	Adverse Events
CEIRS	Centers of Excellence in Influenza Research and Surveillance
CGMH	Chang Gung Memorial Hospital
CGK	Chang Gung Memorial Hospital at Keelung
CHL	Chang Gung Memorial Hospital at Linkou
CHT	Chang Gung Memorial Hospital at Taipei
DMID	Division of Microbiology and Infectious Disease
DOT	Department of Transportation
DCF	Data Collection Form
ED	Emergency Department
EMR	Electronic Medical Record
FWA	Federal-Wide Assurance
g	Gravitational Acceleration
GCP	Good Clinical Practices
HIPAA	Health Insurance Portability and Accountability Act of 1996
IATA	International Air Transport Association
ID	Identification
ILI	Influenza-like Illness
IRB	Institutional Review Board
IV	Intravenous
JH CEIRS	Johns Hopkins Centers of Excellence for Influenza Research and Surveillance
JHH	Johns Hopkins Hospital
JHU	Johns Hopkins University
mL	Milliliter
MOP	Manual of Procedures
NIH	National Institutes of Health
Non-ILI	Non-Influenza-like Illness
NP	Nasopharyngeal
PBS	Phosphate Buffered Saline
PCR	Polymerase Chain Reaction
PI	Principal Investigator
RC	Research Coordinator
REDCap	Research Electronic Data Capture
SAE	Serious Adverse Events
SOM	School of Medicine
SOP	Standard Operating Procedures
SST	Serum Separator Tube
QA	Quality Assurance
QC	Quality Control

1. Study Overview

1.1. Objectives

The overall objective of this study is to improve the ability of the medical and public health infrastructure to respond to influenza pandemics. The specific objectives of the protocol are as follows:

Objective 1: Develop a robust domestic and international influenza surveillance network, which will allow rapid identification of circulating influenza viruses, including those with pandemic potential in human populations.

Objective 2: Create a sample bank of nasopharyngeal and serum samples from patients with suspected and confirmed influenza.

Objective 3: Identify the added benefit of serology when combined with PCR for identification of influenza infections

Objective 4: Characterize the immunologic basis of severe illness due to influenza

1.2. Summary

Accomplishment of the above stated objectives will occur via an international multi-center prospective observational cohort study with both active and passive surveillance components, which will span multiple influenza seasons. The surveillance population will intentionally include those with varying levels of influenza illness, including those managed in the community outpatient setting and those requiring intensive care. This will be accomplished via a mix of active surveillance and passive surveillance.

For the purposes of this study, “influenza season” will begin when Johns Hopkins Hospital has 2 or more positive influenza samples within 7 days, and continue until there have been 3 weeks with no confirmed influenza.

Active Surveillance:

Active surveillance will occur in the emergency department (ED) where individuals present for acute care. For this component, we will recruit both individuals with and without confirmed influenza. We expect to enroll 500 subjects without confirmed influenza each year for the duration of the study with 250 subjects from Johns Hopkins University (JHU) and 250 subjects from Chang Gung Memorial Hospitals (CGMH). These subjects will include those with and without influenza-like illness (ILI). Additionally, we will also recruit subjects who present to the ED and have confirmed influenza A via a clinically obtained laboratory test. We expect to enroll 100 additional influenza A positive subjects each year for the duration of the study with 50 subjects from JHU and 50 subjects from CGMH.

Following informed written consent, enrolled subjects will complete a questionnaire detailing their demographic information, current symptoms, and past medical history. Subjects who do not have confirmed influenza will undergo a nasopharyngeal (NP) swab and subsequent influenza testing with a rapid PCR assay, Xpert Flu and FIA Sofia. For subjects with a positive influenza A result, a nasal wash will also be collected. All subjects will have a blood (serum) sample (10 mL) collected at enrollment. Three to four weeks after enrollment, all subjects will return for a follow up visit where research coordinators (RC) will interview subjects to assess

their initial ED course as well as collect a second blood (serum) sample (10 mL). Should a follow up visit not occur, we will attempt to conduct the interview via telephone. At this time we will also review their medical record to further define their clinical course.

Passive Surveillance:
Passive surveillance will occur through the clinical laboratory, which processes samples for the outpatient, ED, and inpatient populations. Waste material from nasopharyngeal samples (at least 1 mL) testing positive for influenza A and corresponding clinical information will be collected. We expect to enroll 250 subjects each year for the duration of the study with 125 subjects from JHU and 125 subjects from CGMH.

1.3. Clinical Sites

The clinical portion of this study is a collaboration between Johns Hopkins University Hospitals (JHU) in the United States and Chang Gung Memorial Hospitals (CGMH) in Taiwan.

Chang Gung Memorial Hospital (CGMH) is a university-affiliated medical center in Taiwan, with six branches located in varied geographic areas of Taiwan (i.e. northern, central, and southern regions). The three branches that will be included include a tertiary care site, and two regional hospitals with ED census ranging from 20,000 to 180,000. We will conduct surveillance in three of the six emergency departments (EDs) of CGMH around Taipei metropolitan area, Keelung (CGK), Taipei (CGT) and Linkuo (CGL)) with a total nearly 7,000 beds. The CGMH departments of emergency medicine and infectious disease have experience setting up “fever centers”, and conducting clinical and translational studies focusing on emerging viral infections. The CGMH sites covered under this manual of operational procedures are:

CGMH at Keelung (CGK) is a regional hospital with annual ED visits around 75,000. This hospital is the largest medical center in the northeast part of Taiwan, serves as both a tertiary hospital and a primary care facility in Keelung and Taipei metropolitan area. During the past three years (2011-2013), the number of ED visits with clinical diagnosed influenza range from 449 to 1354. This site will perform both active and passive surveillance.

CGMH at Taipei (CGT) is a regional hospital with annual ED visits around 55,000. This hospital located in downtown Taipei area, serves primary as a primary care facility. Patients who need specialized care are routinely transferred to CGL, which is 20 kilometer away from this hospital. The number of ED visits with clinical diagnosed influenza range from791 to 2039 during the past three years. This site will only perform active surveillance.

CGMH at Linkou (CGL) is a medical center with annual ED visits around 180,000. With this huge amount of ED visits, this hospital accommodated around three to six thousand clinically diagnosed and one to two thousand laboratory confirmed influenza infection during the past three years. This medical center has a very diverse patient population in terms of socioeconomic status, medical conditions and ethnicity. This site will perform both active and passive surveillance.

1.4. Training

1.4.1. Study Staff Training

Each research study site has committed to assuring that research staff are properly trained on all aspects of the study including, but not limited to: Health Insurance Portability and Accountability Act of 1996 (HIPAA) regulations of screening and consenting subjects, enrollment procedures, specimen collection and shipping, as well as specimen storage. Certificate of completions for all trainings will be printed and documented in the regulatory binder.

Human Subjects Research Training:
All research staff will be trained in either a web-based or a classroom-based 'research ethics' training model through the CGMH department of research and development before any access to private information is granted. All staff must also successfully complete 'HIPAA and Research' training or equivalent courses provided at CGMH through the same program. The NIH requires all staff to successfully complete their web-based training course 'Protecting Human Research Subjects.'

Biospecimen and Laboratory Training:
All staff using human materials such as blood, internal body fluids, and unfixed tissue will complete annual Bloodborne Pathogen Exposure Control training as mandated by state and federal standards. Those responsible for specimen shipment will complete "Dangerous Goods Shipping" training through courses provided at CGMH in compliance with Department of Transportation/ International Air Transport Association (DOT/IATA) regulations, within the past 2 years.

All coordinators will be trained in sample collection of NP swab, nasal wash, and blood in accordance with CGMH clinical practices and the current clinical training protocols of the CGMH. This training will be a one-day course conducted by an ED nurse educator including didactic, simulation, and observed collection components. Completion of this training will be documented by the nurse educator and recorded in the training log of the regulatory binder.

Coordinators will be trained in basic laboratory techniques as required to perform their duties for this project such as basic specimen processing (centrifuge and aliquoting), and specimen labeling and storage. The central laboratory manager will be responsible for signing off on laboratory training, which will be documented in 'training log' of the regulatory binder.

Institutional Specific Training
All research coordinators will undergo training for the electronic medical record (EMR) currently in use at each institution as well as the REDCap database. All research coordinators will also have to pass a web-based training module including grant and budget application.

Protocol Specific Training
New coordinators will be trained by the site Principal Investigator (PI) and lead Research Coordinator on the details of the study design and protocols. New coordinators will be expected to review and familiarize themselves with the protocol, informed consent documents, manual of

operating procedures (MOP), data collection forms (DCF), and all IRB documentation. The site PI and lead coordinator will educate the new coordinators on the study protocols and procedures, allowing ample time for questions. Prior to beginning independent work, new coordinators will shadow the lead research coordinator for a minimum of 1 week to observe the study workflow and proper procedures before being able to start a shift on their own. The site PI will be responsible for signing off on coordinator's shadowing completion in the "Training Log" of the regulatory binder. Core training on study procedures will be repeated annually and with any changes to the protocol

1.4.2. Clinical Staff Training

Clinical staff training will be provided annually prior the start of influenza season. The site PI will educate clinical staff on the background, objectives, eligibility criteria, procedures and expected outcomes. This education will occur both via in-person presentations, as well additional written follow up for those not in attendance. Both forums will be encouraged to discuss any study-related questions with the site PI.

2. Active Surveillance

2.1. Eligibility Criteria

There will be three populations of patients recruited within active surveillance: Influenza indeterminate symptomatic (N=200), influenza indeterminate asymptomatic (N=50), and influenza A positive (N=50).

Eligibility criteria for influenza indeterminate symptomatic subjects include all subjects 18 years of age or older who present to the study ED sites, whom have 1) fever (reported fever or documented temperature ≥ 38.0°C) and 2) either a cough, headache, or sore throat within the last 7 days.

Eligibility criteria for influenza indeterminate asymptomatic patients include subjects 18 years of age or older who present to the study ED sites whom have not had the following symptoms within the past 7 days: reported fever, documented temperature ≥ 38.0°C, cough, headache, sore throat, myalgia, rhinorrhea or nasal congestion, and/or shortness of breath.

Eligibility criteria for influenza A positive subjects include all subjects 18 years of age or older presenting to the study ED sites who have a positive laboratory test for influenza A from the current ED visit.

Exclusion criteria for all active surveillance subjects include subjects unable to speak and read English or Chinese, unable to provide consent, unable to provide follow-up contact info, currently incarcerated, or previously enrolled in this study.

2.2. Screening

Eligible subjects will be recruited by dedicated research coordinators at the participating EDs 14 hours a day (10am-12am), 7 days a week. Study recruitment may occur via research coordinator initiated or provider initiated pathways.

Research coordinator initiated recruitment: Under a HIPPA waiver, research coordinators will review medical records of patients presenting to the ED with influenza like illness (ILI) or non-influenza like illness (non-ILI) to determine possible eligibility. If a subject is suspected to be eligible for any of the three study populations, a research coordinator will approach the subject's provider to ask if the subject may be eligible, and ask the provider to refer the patient to the study. If the provider indicates the subject would like to hear more on the study, the research coordinator will approach the subject to perform initial screening.

Provider initiated recruitment: Providers will be educated on the study objectives, protocol and eligibility criteria prior to start of the influenza season (see section 2.1). If a provider identifies a subject they suspect may be eligible, they will contact the research coordinator via phone, direct messaging or in person to screen the patient for study inclusion.

Basic presenting, demographic, and eligibility information will be recorded for every patient who is screened for potential enrollment on the Screening and Enrollment Log (See Form 1A). Subjects that do not meet the inclusion criteria will be deemed a screen failure; the reason for their exclusion will be recorded. For those patients who decline participation, the given reason for refusal to participate will be recorded on Form 1A.

Screened patients who meet all inclusion and no exclusion criteria, i.e. who are eligible, will be approached for written informed consent.

2.3. Consent

If an eligible subject indicates they would like to participate in the study, written informed consent will be obtained in a private area such as their assigned room, or a designated research room if they have not been assigned a room yet. In accordance with Good Clinical Practice (GCP), informed consent will be a process in which informed consent will be sought from each prospective subject and appropriately documented. The informed consent form will be signed prior to performing any study procedures. The rights and welfare of the subjects 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.

Although the consent process will be the same for all arms of the active surveillance study, this study includes two different consent forms. Subjects who are influenza indeterminate (i.e. have not received influenza testing) will undergo the consent process with the "Human Influenza Surveillance" consent form. Subjects who have confirmed influenza (i.e. a positive influenza test) will undergo the consent process with the "Influenza Positive" consent form.

Only subjects who are able to give consent are eligible for this study. In order to assess competency, research coordinators will screen subject's medical chart and review for any indicators which may suggest the subjects is not competent. If at any point during the consent process a research coordinator feels a subject is not competent, the research coordinator may either consult the subject's provider to determine competency, or end the consent and enrollment process at his or her discretion. If a subject is deemed not to be competent during

the consent process, the subject will be marked as screen failure on the screening and enrollment log.

Research coordinators will allocate 20-30 minutes for informed consent, but will allow as much time as is needed to ensure the subject has full understanding. Subjects will be provided with a description of the study and the associated benefits and risks and asked to read the informed consent form. After the subject has had time to read the consent form, the research coordinator will ask the subject if they understand the study, and if they have any questions. Subjects will be given an opportunity to ask questions. Once the subject has satisfactory answers to all questions, and indicates that they understand the study, the subject will be asked to sign the consent form. The consenting coordinator will also sign the consent form. The original signed informed consent for will be kept in the corresponding study binder along with data collection forms, and a copy of the consent form will be provided to the subject.

2.4. Enrollment

2.4.1. Eligibility Checklist

Following consent, the research coordinator will complete the eligibility checklist (Form 2A) to ensure the subject is eligible for the study. To complete Form 2A, the research coordinator first identifies the study arm that the potential subject is eligible for. Under the first heading "Inclusion Criteria" the research coordinator need only fill out the section for the arm in which they anticipate enrolling the subject (either influenza indeterminate symptomatic, influenza indeterminate asymptomatic, or influenza A positive). After completing the "Inclusion Criteria" section, the research coordinator then completes the "Exclusion Criteria" section, which is the same for all three arms. Using the information on the "Inclusion Criteria" and "Exclusion Criteria" sections, the coordinator determines if the subject is eligible for the planned arm, and indicates it in the "Eligibility Section". If the subject is eligible the research coordinator moves forward with the enrollment process and assigns the subject a study identification number. If the subject is identified not to be eligible on the eligibility form, they are considered a screening failure and are recorded as such on Form 1.

2.4.2. Study Identification Number

Following informed consent and the eligibility checklist, the subject will be assigned a study identification number and proceed through the enrollment process. The study identification number will include a three letter hospital code followed by a four digit number. The three letter hospital code will be either, CGT for subjects enrolled at Chang Gung Memorial Hospital at Taipei, CGK for subjects enrolled at Chang Gung Memorial Hospital at Keelung or CGL for subjects enrolled at Chang Gung Memorial Hospital Linkou. The first subject enrolled will be 0001, and subjects will sequentially increase throughout the study.

Once the Study Identification Number is assigned, the subject is considered enrolled in the study. The Study Identification Number should be recorded on all data collection forms. For purpose and clarity of this study, all data collection forms for active surveillance will contain the letter 'A' after the form number, and all data collection forms for passive surveillance will contain the letter 'P' after the form number.

2.4.3. Clinical data

For each subject enrolled, research coordinators will complete a set of brief structured clinical data forms to include basic demographic data, vaccination history, exposure history, current symptoms, and past medical history. (See Form 3A: Subject ID and Contact Information; Form 4A: Demographic and Exposure Information; Form 5A: Current Symptoms; Form 6A: Medical History). Data collection must be obtained in a private area such as their assigned room, or a designated research room to ensure patient privacy. To complete Forms 3A-6A, research coordinators will verbally ask the subject each of the listed questions in a step-by-step manner. If a subject is unable to understand or answer a question, this question should be skipped and the remainder of data should be collected. After completion of the clinical data forms, research coordinators will immediately review the subject's past medical history with what is reported in the medical record. Any discrepancy between subjects report and the medical record will be brought to the subject's attention and corrected on the enrollment form as appropriate based upon the subject's report. Any and all corrections made on data collections forms will be made according to the quality management plan (section 4).

2.4.4. Sample Collection

The samples collected from a subject depends if he/she is eligible for this study as an influenza indeterminate subject or an influenza A positive subject.

Influenza indeterminate symptomatic or asymptomatic subjects will be asked to provide

1.) NP swab for influenza testing
2.) Blood (Serum) collection at enrollment
*3.) Nasal Wash at enrollment * ONLY IF SUBJECT IS INFLUENZA A POSITIVE*
4.) Blood (Serum) collection at follow-up visit.

Influenza A positive subjects will be asked to provide:

1.) Nasal wash at enrollment
2.) Blood (Serum) collection at enrollment
3.) Blood (Serum) collection at follow-up visit

Research coordinators will be responsible for ensuring collection of NP swabs, nasal washes, and blood (serum) samples (10 mL per sample) either through collecting it themselves or coordination with clinical staff. All research coordinators will be trained for sample collection (See section 1.4.1). As each sample is collected the research coordinator will fill out the appropriate form documenting collection (see Form 7A Enrollment Specimen Collection). Please refer to section 5, Biological Specimens, below for more information on procedures for specimen collection, processing, labeling, handling, tracking, and shipment.

2.4.5. Influenza Testing

Note, this section does not apply to the influenza positive subjects

All influenza indeterminate subjects will undergo influenza testing using the FIA Sofia and Cepheid GeneXpert. Upon enrollment, a NP swab will be collected, placed in universal transport media, and labeled according to study protocol (see section 5.1 for sample collection instructions). The sample will then be placed in a red STAT bag and transported to the virology laboratory by the research coordinator. Via a pre-approved lab requisition order by the site PI,

the research coordinator will obtain SOFT ID labels from microbiology lab. These labels create a barcode to attach to the specimen vial and Gene-Xpert cartridge to ensure proper identification of cartridge and specimen in the event there are multiple tests running at the same time. Once labels are obtained, the research coordinator will hand off the specimen to virology laboratory personnel whom will run the sample on the both FIA Sofia and Gene-Xpert machine and call results to the research coordinator's study cell with the results. The lab personnel will also scan the results into the subject's medical record. The research coordinator will then report the results verbally to the subject and the subject's provider. The target turn-around time from specimen collection to result is 2 hours. In the event a research coordinator cannot deliver these results to the provider in person (e.g. provider is busy with a trauma or critically ill patient), a note will be made on the enrollment log, and provider will be informed as soon as possible. Additionally, the influenza test results will be made available to the provider through the EMR.

If a positive influenza A test result returns and the subject has left the ED, the research coordinator will immediately attempt to contact the subject via the contact telephone number provided, to inform them of the test result. If the test is positive for influenza A, the coordinator will ask the subject to return to the ED for the nasal wash and any further treatment that may be indicated. Additionally, the research coordinator will inform the patient's provider of the influenza test result so that he/she may decide if the patient requires further contact and/or treatment. If the treating physician is no longer available, the research coordinator will contact the site PI.

2.4.6. Enrollment Completion

At the completion of the enrollment process subjects will be compensated $15 in the form of a gift card. All gift card transactions must be logged with the last 4 digits of the gift card and the initials of the subject as well as initials of the research coordinator dispensing funds.

At the time of compensation, the subject will be asked to make an appointment for the follow up visit in 21-35 days from the date of enrollment. An appointment card will be given to the subject to remind them of the follow up visit (Appendix 2). One phone call will be made 1 week prior to the 3 week visit to remind the subject of this visit. If the subject is unable to make a follow up appointment at the time of enrollment, they will be contacted starting 5 days after enrollment to arrange a follow up appointment.

2.5. Follow Up

Each subject will have a follow-up ED visit 21 – 35 days following their enrollment. They will receive an appointment reminder card at the time of enrollment with instructions on where to wait, and the telephone number to the study cellphone.

Research coordinators will call subjects one week prior to their scheduled appointment as a reminder. If the subject misses their appointment, up to 3 additional phone calls may be made to remind the patient to come in or to complete a phone interview. When the subject presents for the follow up visit, the subject will be asked the follow up visit questions (Form 8A Follow-up Assessment) and a blood (serum) sample (10 mL) will be collected. Subjects who return to the study site will receive a $30 gift card in compensation. This must be logged in to the Gift Card Log (Appendix 3). All gift card transactions must be logged with the last 4 digits of the gift card and the initials of the subject as well as initials of the research coordinator dispensing funds.

If the subject is unavailable for an in-person interview and blood (serum) collection, a phone interview will be conducted. The phone interview will use the script provided on Form 8A (Follow up Assessment). Only subjects who present to the study site will be compensated since all dispensed funds must be signed for.

2.6. Contact Monitoring

Active surveillance subjects will be contacted no more than 4 times. The first call will be one week before the appointment date; this call may be made at any time between 10am-8pm and recorded in Form 8A.

The day after a missed appointment, 3 consecutive calls within 3 days will be made. These 3 calls should be made at different hours of the day (for example, the first call in the morning, the next day in the afternoon and the third day in the evening.) If unsuccessful, subjects may be categorized as “unavailable for follow up” if 1) there are a minimum of 4 failed contact attempts, 2) the provided contact numbers are non-functional, or 3) The subject requests no further contact from the study. All attempts made to a subject must be recorded on the Follow Up Log.

All attempts to contact the subject will be recorded on Form 8A and the Follow Up Log with date and time.

2.7. Chart Review

Chart Review is to occur for all active surveillance subjects no earlier than 28 days after the date of subject enrollment. Chart review will capture the ED treatments, visits, outpatient visits or hospitalizations, and other follow up doctor’s visits noted in the medical center’s EMR to include the subject’s presentation, treatments, and course of medical visits made within 21 days of subject enrollment (See Form 9A ED Chart Review and Form 10A Inpatient Chart Review).

2.8. Withdrawal

A subject is considered enrolled after they sign the informed consent form and are assigned a study ID number. A subject is made aware during the consent process that he or she is free to withdrawal from the study at any point during their study period, but information that has already been captured up until the moment they withdrawal can still be used for research purposes. All withdrawals will be recorded on the withdrawal form (See Form 11A: Withdrawal Form) and included in the every other week enrollment report form (See Form 13A: Enrollment Report). For this study, it is not necessary to replace withdrawn subjects for new subjects. The process of withdrawal may be made verbally, in person, over telephone, or in writing via email or fax by the subject. Subjects will not need to complete any paperwork to be considered withdrawn. Research coordinators will document these withdrawal subjects using the withdrawal form.

2.9. Enrollment Target

We expect to enroll 300 subjects through the active surveillance arm at CGMH: 200 symptomatic influenza indeterminate subjects; 50 asymptomatic influenza indeterminate subjects; and 50 influenza A positive subjects. The site PI is responsible for monitoring subject enrollment on a monthly basis. If the site PI suspects enrollment targets are significantly below

what is expected during the particular time in influenza season, corrective action will be taken, please see section 6.

3. Passive Surveillance

Passive surveillance will occur through the clinical laboratory, which processes samples for the outpatient, emergency department, and inpatient populations. Waste material from nasopharyngeal samples (at least 1 mL) testing positive for influenza A and corresponding clinical information will be collected. The clinical information will be linked with the nasopharyngeal samples through an anonymous study ID.

We expect to enroll 125 subjects each year for the duration of the study through passive surveillance. Using the corresponding epidemiologic information, NP samples will be selected based on their potential for novel or severe infection to move forward for further characterization.

3.1. Eligibility

Eligible subjects include all patients who tested positive for influenza A at Chang Gung Memorial Hospital, and have enough waste sample (at least 1 mL) available for research purposes.

3.2. Screening

Study research coordinators will identify subjects by contacting the clinical laboratories at least once a week to identify NP samples positive for influenza A with appropriate volumes of waste NP sample. All eligible patients will be recorded on the enrollment log (Form 1P: Enrollment Log), and eligibility criteria will be documented on Form 2P: Eligibility Checklist).

3.3. Waiver of Consent

This is a retrospective study which utilizes information and NP samples which were primarily collected for clinical purposes and is of minimal risk. Subjects will be enrolled under a waiver of consent, as it is not feasible to consent subjects due to the retrospective nature of this study.

3.4. Study Identification Number

Each eligible subject will be documented on the Passive Surveillance Enrollment Log and assigned a study ID. The study identification number will include a three or four letter hospital code followed by a three digit number. The four letter hospital code will be one of the following:

PCGT for subjects enrolled at Chang Gung Memorial Hospital at Taipei,
PCGK for subjects enrolled at Chang Gung Memorial Hospital at Keelung or
PCGL for subjects enrolled at Chang Gung Memorial Hospital Linkou.

The first subject enrolled will be 0001, and subject numbers will sequentially increase throughout the study.

3.5. Chart Review

Chart review is to occur for all passive surveillance subjects no earlier than 28 days after the day the influenza A positive NP (waste) sample was originally collected. Chart review will capture the ED visits, outpatient visits or hospitalizations, and other follow up doctors' visits noted in the medical center's EMP to include subject's presentations, treatments, and course of medical visits made from 1 day prior to the day the influenza A positive NP (waste) sample was collected until 21 days after the day the influenza A positive NP (waste) sample was collected. The outpatient, ED, or Hospital visit at which the influenza A positive NP (waste) sample was collected will be considered the index visit for the subject. This visit will be used to complete the Demographics and Vaccination Information (Form 4P), Current Symptoms (Form 5P) and Medical History (Form 6P). The patient's medical course will be detailed through the index and subsequent outpatient, ED and hospital visits and recorded in the corresponding forms (See Form 9P ED/Outpatient Chart Review, and Form 10P Hospitalization Chart Review)

3.6. Sample Processing

Please refer to section 5.1.4 for additional information on how the waste NP samples will be processed. Form 7P: Waste Sample Collection should be filled out for each sample processed.

3.7. Enrollment Target

We expect to enroll 125 subjects each influenza season through passive surveillance.

4. Data Management

All hard copies of data collected from subjects will be kept in study binders which will be kept in a secure cabinet.

Each active surveillance study binder will contain A-Z tabs in which each tab corresponds with one subject. Therefore, there will be 26 subject IDs per one binder. Every subject's data collection forms will be housed in a binder tab. Every section should include a signed written consent form, data collection Forms 2A-12A, Form 14A (if randomly selected for 10% QA), Form 16, as well as a note if a protocol deviation form was filed for the subject.

Each passive surveillance study binder will contain A-Z tabs in which each tab corresponds with one subject. Therefore, there will be 26 subject IDs per one binder. Every subject's data collection forms will be housed in a binder tab. Every section should include, data collection forms 2P-12P, Form 14P (if randomly selected for 10% QA), as well as a note if a protocol deviation form was filed for the subject.

Data collection forms will be completed in hard copy by the research coordinator in blue or black pen only and in legible print only. Should a correction be needed, a single line will be crossed through the mistake, and the correction will be made next to the mistake. The research coordinator who made the correction must initial and date on the margin of the form. All fields must be completed unless subject refused to answer, in which a note should be made in the comments section of that form. If a data field is left blank because no data is available (for example, initial vitals not taken in the ED), then the research coordinator should enter "999" for the data collection field. Any data entries captured as "999" will be understood as data field not captured; this will prevent any data field from being left blank on accident.

4.1 REDCap

The research coordinator who collected the information from a subject on data collection forms should be the one to also enter this data into the REDCap system (http://project-redcap.org/), a 21CFR11 compliant, secure encrypted database. Only de-identified information will be entered in the electronic database, identified by the unique study ID number only. Only authorized study team members will be granted access to the study data.

To ensure data management, all research coordinators must initial the excel document housed in a secure computer drive named “Form 15A QC Checklist” for the active surveillance arm, or “Form 15P Data Review Checklist” for the passive surveillance arm in real time. These excel spreadsheets ensure that no research coordinator performs quality control on their own work. The spread sheet will document which coordinator collected data on hard copies, which coordinator entered information into REDCap, and on which items a coordinator has performed QC.

4.2 Staff Communication

In order to maintain communication amongst the team, there will be 3 methods of monitoring enrollment and study procedures throughout the clinical phase of the study.

Nightly Email: Everyday, at the close of night shift, the research coordinator is responsible for sending out a nightly email to the study team with a review of the day’s shifts. This email should include the date, number of patients screened, number of patient’s eligible, number of subjects enrolled, as well as a notes section. The note section should not be used to replace any reporting that is required per IRB or DMID regulations, but serve as a place to update other study staff members if any concerns from shift arise such as protocol deviations.

Weekly Surveillance Meeting: Weekly surveillance meetings may take place in person or via telephone conference.

Monthly Administrative Core Meeting: A monthly administrative meeting takes place once a month in person and is led by the site PI. At this meeting a review of the previous month’s meeting is discussed if any further concerns linger or require continued discussion. A monthly subject enrollment summary is discussed to ensure enrollment targets are being met. Review of any protocol deviations for the month and the corrective actions are discussed. Updates on this month’s quality assurance 10% review is discussed as well in case any patterns or concerns that arise.

5. Biologic Specimens

5.1. Sample Collection and Processing

This section provides information to study staff members regarding the collection, processing, and transportation of clinical specimens to their proper destination. It is essential that these guidelines be followed without deviation to ensure specimen integrity is maintained. Biological specimens are to be collected in accordance with Universal Precautions guidelines.

All research coordinators will undergo 3 sample collection trainings: nasopharyngeal swab, blood (serum), and nasal wash, as outlined in the training section (Section 1.4.1).

5.1.1. Nasopharyngeal Swab

For each influenza indeterminate subject eligible for active surveillance, a nasopharyngeal (NP) flocked swab will be collected and carried in universal transport media. **All research coordinators collecting NP swabs should undergo appropriate training as required by each institution.**

NP Swab Collection procedures:

1. Put on mask and gloves.
2. Have subject sit with head against a wall or stabilize the head with your hand if a wall is not accessible. Subjects have a tendency to pull away during this procedure.
3. Remove the cap and insert swab into one nostril straight back (not upwards) and continue along the floor of the nasal passage for several centimeters until reaching the nasopharynx (resistance will be met). The distance from the nose to the ear gives an estimate of the distance the swab should be inserted. Do not force swab, if obstruction is encountered before reaching the nasopharynx, remove swab and try the other side.
4. Rotate the swab gently for 5-10 seconds to loosen the epithelial cells.
5. Remove swab and place in universal transport media. Reattach the cap securely, label swab and place in a red STAT bag.

Immediate NP Processing:

The sample should be promptly transported to the virology lab within 30 minutes of collection in CGL and CGK, within 60 minutes in CGT, where the sample will be sent to CGL for processing. If unanticipated events arise in which sample cannot be transported to virology lab within 30 minutes for processing, the sample should immediately be placed in the temporary specimen fridge in the adult ED until a research coordinator is able to transport sample.

Following sample collection, clinical laboratory personnel will process the sample and perform influenza testing with the FIA Sofia and Cepheid Gene-Xpert. A study requisition will be made available for all NP swab samples in order to obtain SOFT ID labels from microbiology lab. These labels will be placed on the original specimen vial, the lab requisition form, and on the panel.

Final NP Processing and Storage:

The remaining 2.5 mL of sample will be aliquoted into micro tubes and stored by clinical laboratory personnel according to laboratory SOP. Once a week, remaining NP swab material should be picked up from the clinical laboratory freezers and transported to the Central laboratory in CGL and CGK where it will be logged, labeled and stored according to SOP of the Central laboratory in CGMH .

5.1.2. Blood (Serum)

For each active surveillance subject, blood (serum) will be collected. **All research coordinators collecting blood (serum) should undergo appropriate training as required by each institution**. If the clinical staff agrees to collect the study sample, this is permissible. If the clinical staff is not collecting the required blood, then the research coordinator should collect the required blood either through an existing IV, or venipuncture (detailed below).

Blood (serum) collection procedures:

1. Select a suitable site for venipuncture, by placing the tourniquet 3 to 4 inches above the selected puncture site on the patient.
2. Put on mask and gloves and palpate for a vein.
3. When a vein is selected, cleanse the area with alcohol in a circular motion, beginning at the site and working outward. Allow the area to air dry. After the area is cleansed, it should not be touched or palpated again. If you find it necessary to reevaluate the site by palpation, the area needs to be re-cleansed before the venipuncture is performed.
4. Ask the subject to make a fist; avoid “pumping the fist”. Grasp the subject’s arm firmly using your thumb to draw the skin taut and anchor the vein. Swiftly insert the needle through the skin into the lumen of the vein. The needle should form a 15-30 degree angle with the arm surface. Avoid excess probing.
5. When the tubes are filled, remove the tourniquet. Place gauze on the puncture site and remove needle from subject’s arm.
6. After holding pressure for 1 minute, apply a Band-Aid to puncture site.

For the purposes of this study 10 mL of blood should be collected in serum separator tubes (SST). Up to 3 attempts may be made to draw blood. After 3 failed attempts, we will document the blood (serum) sample collection form as “unable to obtain” and record reason in the space provided.

Immediate Blood (Serum) Processing (same for CGT, CGK and CGL)

1. Following collection, tubes will be immediately labeled and inverted 3 times, kept upright at room temperature (20-25°C) for a minimum of 30 minutes to allow for clot to form.
2. After 30 minutes the tube should be placed upright in the refrigerator (2-8°C) for storage.

At the end of the day, collected blood should be transported to the Central laboratory in CGMH on ice for final processing and storage.

Final Blood (Serum) Processing and Storage:

1. Upon delivery to Central laboratory in CGMH, the Research Coordinator will document the blood specimen on the Central laboratory in CGMH Specimen Tracking Log.
2. Centrifuge the SST containing the clotted blood specimen at 1100-1300 x g for 10-15 minutes at room temperature (20-25°C).
3. Use a sterile pipette to aliquot the serum into as many 0.5 mL aliquots as possible.
4. Each serum aliquot will be placed into an appropriately labeled screw cap micro tube.
5. All serum aliquots will be stored at -80°C in the Central laboratory in CGL and CGK Repository and disseminated to research projects per or Central laboratory in CGMH SOP.
6. The Research Coordinator or a CGL and CGK designee will document all serum aliquots to be stored at -80°C in the Central laboratory in CGL and CGK Repository on the (or Central laboratory in CGL and CGK Specimen Storage Log).
7. The Central laboratory in CGL and CGK will document and track all blood specimens and serum aliquots using Laboratory Specimen Tracking Logs, Laboratory Specimen Storage Logs, and a Laboratory Freezer Inventory Tracking System.

5.1.3. Nasal Wash

For each influenza A positive subject in active surveillance (whether through the influenza indeterminate or influenza A positive pathway), a nasal wash sample will be collected. **All research coordinators collecting nasal wash samples should undergo appropriate training as required by each institution**.

Nasal wash sample collection process:

1. Put on mask and gloves.
2. Have subject sit straight up with head tilted back 45 degrees.
3. Give subject sterile cup to hold under their nose.
4. Squirt entire saline packet (1 mL) into one nostril and allow subject to put head straight and lean forward to allow wash to drip into cup.
5. Repeat step 4 for other nostril wash collection.
6. Store NP wash in the refrigerator (2-8°C).

At the end of the day, collected NP wash should be transported to the Central laboratory in CGL and CGK on ice for final processing and storage.

Final NP Wash Processing and Storage:

1. Upon delivery to Central laboratory in CGL and CGK, the Research Coordinator will document the NP wash specimen on the Central laboratory in CGL and CGK Specimen Tracking Log.
2. The Research Coordinator or a CGL and CGK designee will process the NP wash specimen as follows:
    a. If necessary, break cell clumps apart by gently pipetting the NP wash specimen up and down.
    b. Centrifuge the NP wash specimen at 450 x *g* for 10 minutes at 4°C.
        <u>Note:</u> Occasionally lots of mucus is present. If so, a second centrifugation may be necessary after pipetting the NP wash specimen up and down.
    c. Use a sterile pipette to aliquot NP wash supernatant into as many 0.5 mL aliquots as possible.
        i. Each NP wash supernatant aliquot will be placed into an appropriately labeled screw cap micro tube cryovial.
        ii. All NP wash supernatant aliquots will be stored at -80°C in the Central laboratory in CGL and CGK Repository and disseminated to research projects per Central laboratory in CGL SOP.
    d. Use a sterile pipette to resuspend NP wash cell pellet in PBS and perform cell count.
        <u>Note:</u> If the mucus/cells are not "packing" following the centrifugation, add 5 mL PBS (cold is better), pipetting up and down. Repeat centrifuge step. The additional PBS wash is often sufficient.
    e. Centrifuge NP wash cells at 450 x *g* for 5 minutes at 4°C.
    f. Use a sterile pipette to resuspend NP wash cell pellet in freezing medium by storing $1x10^6$ cells per 1 mL of freezing medium.
    g. Use a sterile pipette to transfer NP wash cells with freezing medium into 0.5mL aliquots.
        i. Each NP wash cells aliquot will be placed into an appropriately labeled screw cap micro tube cryovial.

ii. Place NP wash cells aliquots in “Mr. Frosty” container and move to -80°C freezer.
iii. All NP wash cells aliquots will be stored at -80°C in the Central laboratory in CGL and CGK Repository and disseminated to research projects per Central laboratory in CGMH SOP.

3. The Research Coordinator or Central laboratory in CGL and CGK designee will document all NP wash specimens, NP wash supernatant aliquots, and NP wash cells aliquots to be stored at -80°C in the Repository on the CGL and CGK Central Laboratory Specimen Storage Log.
4. The will document and track all NP wash specimens, NP wash supernatant aliquots, and NP wash cells aliquots using Laboratory Specimen Tracking Logs, Laboratory Specimen Storage Logs, and a Laboratory Freezer Inventory Tracking System.

5.1.4. Waste NP material

Waste material from clinically collected nasopharyngeal samples will be collected for the passive surveillance option. These leftover nasopharyngeal samples will be collected from the clinical laboratory and transported to the Central laboratory in CGL and CGK on ice. These samples may come from NP swab, NP wash or bronchoaveolar lavage (BAL) specimens.

Waste NP Processing

1. Upon delivery to Central laboratory in CGL and CGK, the Research Coordinator will document the waste NP swab specimen on the Central laboratory in CGL and CGK Specimen Tracking Log.
2. The Research Coordinator or Central laboratory in CGL and CGK will process the waste NP specimen as follows:
    a. Vortex the waste NP swab specimen vigorously for 5 seconds.
    b. Use a sterile pipette to aliquot the NP swab specimen into as many 0.5mL aliquots as possible.
        i. Each waste NP swab aliquot will be placed into an appropriately labeled screw cap micro tube.
        ii. All aliquots will be stored at -80°C in the Central Laboratory CGL and CGK Repository and disseminated to research projects per CGMH SOP.
3. The Research Coordinator or designee will document all waste NP swab aliquots to be stored at -80°C in the Central laboratory in CGL and CGK
4. The Central laboratory in CGL and CGK will document and track all waste NP swab specimens and NP swab aliquots using Laboratory Specimen Tracking Logs, Laboratory Specimen Storage Logs, and a Laboratory Freezer Inventory Tracking System.

5.2. Sample Labeling and Handling

All safety guidelines of the local safety committee and/or institutional policies for handling biological specimens must be followed. Universal Precautions guidelines are to be observed.

Sample Labeling

Research coordinators are responsible for labeling all specimens at the time of collection directly on the tube or cup (depending on the type of sample). Specimen labeling should include study ID, date of collection, time of collection, and initials of coordinator who collected sample. (See Appendix 1).

For each sample collected, an individual sample sheet documenting time and date of collection and processing should be collected. Please refer to the corresponding forms: Form 7A for active surveillance enrollment, Form 8A for active surveillance follow up, and Form 7P for passive surveillance. In addition, Form 16: Specimen Quality Control Checklist should be completed for each subject and placed in their binder tab. This form is found under the Active Surveillance Forms, however, it is used for both active and passive surveillance arms.

Sample Shipping
Samples will then be shipped in bulk from CGL to the JH CEIRS central laboratory. When shipping samples to the JH CEIRS laboratory, shipments will be made per the institutions environmental safety regulations.

6. Quality Control and Quality Assurance

Following a written DMID-accepted site clinical quality management plan, the site is responsible for conducting routine quality control (QC) and quality assurance (QA) activities to internally monitor study progress and protocol compliance. The Principal Investigators will provide direct access to all study-related field sites, source documents, and reports for the purpose of monitoring and auditing by the sponsor, and inspection by local and regulatory authorities. The Principal Investigators will ensure all study staff are appropriately trained and applicable documentations are maintained on site.

Quality management tools include forms 12A-16A for the active surveillance arm and 12p-16P for passive surveillance arm which will be used for quality control and quality assurance purposes by all study staff members delegated. If at any point during quality control or assurance a pattern of inconsistencies should arise, then the data manager, lead research coordinator or site PI should make a note in the regulatory binder, and a plan for corrective action should be discussed at monthly administrative meetings.

Enrollment Target: Each site will prepare an enrollment report every other week during the enrollment period to ensure timely and accurate enrollment of potential subjects (See Form 13A for active surveillance and Form 13P for passive surveillance). This report will be sent to the site PI for review and discussion at the monthly administrative core meeting.

Inclusion/Exclusion Criteria Check: For each enrolled subject, the research coordinator will check the inclusion and exclusion criteria to ensure each subject is eligible for progression in the study. For active surveillance subjects this is documented on Form 2A: Eligibility Criteria.

Document Completion: For each enrolled subject, a checklist will be completed (See Form 12A for active surveillance and Form 12P for passive surveillance) to ensure completion of all study procedures and forms.

Data Entry and Quality Control Check: Verification of data entry and quality control check will be tracked in an excel spread sheet (From 15A for active surveillance and 15P for passive surveillance) which will be housed in a secure drive where only study staff will have access to it. This form is used to record which data forms a coordinator collected, as well as which coordinator entered data into REDCap by entering research coordinator's initials in corresponding boxes. This will help ensure that no research coordinator performs quality

control on their own work. This spreadsheet will be updated in real time as data forms are collected and entered into REDCap. At the end of the enrollment period, the clinical data manager will be responsible for signing off on the final version, ensuring that all data collection forms are completed, all forms have been quality control checked, and all documents have received quality control as indicated.

Data Accuracy Check: For a randomly selected 10% of the enrolled subjects, all data forms and data entry will be checked by the lead research coordinator to ensure appropriate data collection. Form 14A for active surveillance and form 14P for passive surveillance is to be completed by the research coordinators once a month on 10% of random enrolled subjects during a one month period. During months when enrollment is low due to fewer cases of suspected influenza, at least 4 subjects per month must be checked for monthly quality assurance, to ensure integrity. Either 10% of enrolled subjects for the month or 4 subjects (whichever number is greater) must be checked for quality assurance. The research coordinator is responsible for ensuring what is on a subject's medical records matches what is captured on data collection forms, and what is captured on data collection forms is what is captured in REDCap. Should any inconsistencies arise, they should be recorded on form 14A or 14P. If it is determined that the original data recorded on a DCF is incorrect, both the hard copy DCF and the electronic database must be updated to reflect the change.

Data Completion Check: All data entered into the REDCap system will be evaluated every other week by the data manager for completion, accuracy and logic. Missing, incomplete or out of field data elements will be reported back to the site PI and lead research coordinator to resolve with their study personnel within 1 week of receipt.

Specimen Quality Control Checklist. This documents correct specimen collection, handling, and storage. This form (Form 16) is to be filled out on every subject in both the active surveillance and the passive surveillance arms. The research coordinator is responsible for initialing the form when he or she completes a task to ensure proper data management of the specimens.

Final Data Completion Check: At the end of the study period, the clinical data manager is responsible for signing off on the data management, accuracy and integrity. It is then the responsibility of the site PI to accept or sign off on the data of the study by entering a note in the regulatory binder.

7. Protection of Human Subjects

In accordance with Taiwan IRB regulations, DMID regulations, and Good Clinical Practice regulation, this study is in agreement with adhering to all institution's regulations protecting human subjects for this study.

7.1. IRB

Per regulations and prior to enrollment of subjects into this study, Taiwan Institutional Review Boards will provide initial and continuing reviews of this research study. The study protocol, the associated informed consent documents, and any written information given to study subjects, will be reviewed and approved by the appropriate IRBs listed on their respective FWAs. Any amendments to the protocol, consent documents, or written information for subjects will be

reviewed and approved by the Chang Gung Memorial Hospital Medical Institutional Review Boards before they are placed into use.

7.2. Adverse Events

The Principal Investigator at will be responsible for monitoring and oversight of problems/events with implementation of this study. Serious adverse events (SAE) are the highest of three severity levels for protocol deviations, followed by major event and minor event. A serious adverse event is characterized as an event that results in death, is immediately life threatening, requires inpatient hospitalization, results in significant disability, is a congenital anomaly, or is an important medical event.

Due to the nature of this research study, it has been determined that AEs and SAEs will not be collected or reported to the IRB or sponsor since this is a low risk study.

7.3. Protocol Deviations

A protocol deviation is any noncompliance with Good Clinical Practice or protocol-specific Manual of Procedures. The noncompliance may be either on part with the subject, the site principal investigator, or the study site staff. It is the responsibility of the site principal investigator and other study personnel to use continuous vigilance to identify and report protocol deviations. The site principal investigators and other study personnel are responsible for knowing and adhering to their IRB requirements. Only protocol deviations that are related to subject safety and/or eligibility will be reported to the local IRB/IEC per its guidelines. Line listings of protocol deviations that are reported to the IRB will be submitted to DMID on a quarterly basis.

Depending at which level of study staff the protocol deviation is identified, it should be reported to the clinical research manager and then to the site principal investigator. The time urgency at which deviations should be reported to principal investigators depends on the severity of the deviation which is broadly and vaguely defined by DMID. The following guidelines should be used when identifying the severity of a protocol deviation and defining the urgency at which the deviation should be reported to the site PI:

Instrument deviation: When instruments used for specimen storage or processing fail to work and the samples are no longer viable samples, this deviation would be considered a major protocol deviation. Because the loss of samples is in direct conflict with this study's objectives, this deviation must be reported immediately to the site PI so immediate action can be taken to prevent any further loss of samples.

Subject deviation: When a subject is presented with more than a minimal risk, a major protocol deviation is identified and must be reported to the site PI, IRB and DMID within 24 hours of identification.

Quality management deviation: When quality management tools are not being captured properly or during the time frame indicated in this MOP, but it is determined that no patient care is affected nor are study objectives in jeopardy, then this deviation is considered minor.

Study staff deviation: If study staff members are incorrectly performing data collection according to this MOP, or collecting data on outdated forms, this is considered a minor deviation.

Because this is a minimal risk study and no more than minimal risk is expected, all study staff members hired for this study are expected to use good judgment and common sense, should an unexpected event occur and require official documentation.

Appendix 1: Data Label

CEIRS SURVEILLANCE

Study ID: _____

Date Collected :_____

Specimen :_____

Coordinator Initials:_____

Appendix 2: Appointment Reminder Card

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謝謝您參加這個”流行性感冒監測研究計劃”!
我們需要您在_____年_____月_____日上午／下午回來進蹤，
花費的時間不會超過 45 分鐘，而我們會再多採集 10mL 左右的血液檢查。
您的車馬費及時間補償將是 _________元。

回診指引：
請不要掛號，到等候室之後致電(03)3281200-3531 讓我們知道您已抵達，
研究助理會在 5 分鐘左右來找您。

Appendix 3: Gift Card Log

Study ID#	Gift Card #	Patient Name	Patient Initials	Employee Dispensing Funds	Notes

Appendix 4: Immunosuppressive Medications

Glucocorticoids: *Chronic oral or intravenous corticosteroid therapy (defined as the equivalent of 10 mg of oral prednisone per day or greater for longer than 2 weeks)*

- Betamethasone
- Cortisone
- Dexamethasone (Decadron)
- Hydrocortisone (Cortef)
- Methylprednisolone (Medrol)
- Prednisone

Antibodies

- Abciximab (ReoPro)
- Adalimumab (Humira)
- Basiliximab (Simulect)
- Daclizumab (Zenopax)
- Infliximab (Remicade)
- Rituximab (Rituxan)

azathioprin (Imuran)

cyclosporin (sandimmune, Neoral)

etanercept (Enbrel)

hydroxychloroquine (Plaquenil)

lefunomide (Arava)