

Supporting Statement B for

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

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Introduction

Only limited detail will be provided, but the IRB protocol is in the “supplemental documents” section of the ROCIS entry, called “Attachment 2 Clinical Protocol #14-0076 ”

B.1 Respondent Universe and Sampling Methods

The specific objectives of the protocol (Attachment 2) are as follows:

- To 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.

- To create a sample bank of nasopharyngeal and serum samples from patients with suspected and confirmed influenza.
- To identify the added benefit of serology when combined with PCR for identification of influenza infections.
- To characterize the immunologic basis of severe illness due to influenza.

The estimated respondents per year are 300 subjects per country. Additionally per year, we will obtain 125 samples per country to enrich our study for a total of 425 subject per country. The estimated respondents per year are 850 subjects for all sites combined (Please see attached Explanation for Sample Size at the end of this document). Below are estimated demographic data on the subjects. This protocol intends to enroll based on previous years demographic data. Enrollment will occur at acute care hospitals across national capital regions of the US (Baltimore Washington DC) and Taiwan (regional hospitals around Taipei).

	Johns Hopkins University and affiliates	Chang Gung University and affiliates	Total Per Year
Male	212	213	425
Female	213	212	426
African American	272	0	272
Caucasian	128	0	128
Hispanic	20	0	20
Asian	5	425	430
Total	425*	425*	850

***Of note, the number of subject per site (n=425 per year) appears different in Statement B than in Statement A. This is because Supporting Statement A provides details for active recruitment only (n=300 subjects per site). Statement B includes active (n=300 per site) and passive subjects (n=125 per site). Passive sample collection requires no direct patient interaction or burden.**

This study will be inclusive of all individuals who meet the Subject Inclusion/Exclusion Criteria, regardless of religion, sex, or ethnic background. Please see table above for estimated gender and racial demographic break down across sites. This study does not aim to generalize a population. Hence, there is not a specific sample size calculation for this surveillance population, but smaller sample size calculations have been performed for the laboratory analysis associated with serologic and immunologic studies. There is no stratification variable, the first 850 (425 per site) eligible subjects per year will be enrolled.

Based on historical experience with similar studies at these sites we expect equal enrollment and response rates across all subgroups. We anticipate a retention and

completion rate for the follow-up visit of at least 85% based on our historical experience which supports the needs for our sample size.

B.2 Procedures for the Collection of Information

The surveillance population will intentionally include those with varying levels of illness severity from influenza, including those with local cluster outbreaks managed in the community outpatient setting, to those with acute respiratory symptoms requiring intensive care from each of the regional hospital networks. EDs are widely recognized as the clinical venue where patients most frequently seek care during the surge associated with severe pandemics. They serve as the primary site for initial evaluation and treatment for patients who are ultimately hospitalized with influenza each year and are responsible for the care of patients with influenza related illnesses who are treated and discharged.

Investigators are faculty members and providers to patients in these clinics, and thus have an existing clinician-patient relationship. Accordingly, they are readily available to determine eligibility for study participation. Eligible subjects for the active surveillance group will be recruited by dedicated trained research coordinators at the participating EDs. They identify potential participants using the medical record. When a potential subject is identified, he/she will be asked to consent for screening to determine eligibility. If the subject consents and is eligible and willing to participate, then study staff shall proceed with the written informed consent process (Attachments 3-6).

(Attachments 3-6) Written informed consent will be obtained in a private patient room in compliance with HIPAA regulations. Subjects will be provided with a description of the study (purpose and study procedures) and asked to read and sign the informed consent form. For each enrollee, research coordinators will complete a set of brief structured clinical data forms to include basic demographic data, vaccination history, co-morbid illness, initial vital signs and history of present illness. To complete this set of forms, study coordinators will verbally ask each subject to respond to the listed questions in a step-by-step manner. 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.

Immunologic analysis will be performed on all patients with positive PCR influenza tests. We will enroll 180 PCR influenza positives subjects each year. Immunologic outcomes will be assessed based on disease severity, with an estimated breakdown of 5% severe disease, 40% moderate disease, and 45% mild disease each season. With these distributions we will accrue 54 patients (in the smallest or severe group) over the course of 6 influenza seasons a sample size sufficient to permit analysis and characterization of differences between the groups. Changes in multiple factors that correlate with disease will be the primary analysis.

Serologic analysis will be performed on 200 patients including: 1) Those with no clinical symptoms (N=100); 2) those with ILI and evidence of lower airway disease defined as diagnosis of pneumonia (N=40); 3) those who ILI and severe disease resulting in ICU admission, mechanical ventilation or death (N=10) and; 4) randomly selected ILI samples from the remaining subjects (N=50). Serologic analysis will be performed on groups 1-4. Based on our estimated prevalence data from our population, we anticipate that 20 of these (i.e. 20% of those from groups 2-4) will have positive PCR influenza tests. With these numbers, we anticipate that serologic analysis of each of the 4 groups will permit us to detect the added value of serologic testing when combined with PCR for identification of influenza infections. By definition, changes of four fold or greater in antibody titer at 28 days post infection compared to the titer at time of presentation is considered to be a positive response to influenza infection and will be used as the criteria for judging a positive result.

Influenza virus genome sequencing will be performed on all influenza positive samples collected from both the immunological and serological study groups. Specific genotypes will be correlated with the clinical disease descriptions described above.

The following bullet points explain what information/data will be collected from subjects by a fully trained staff member known as a research coordinator (RC). All subjects will be enrolled for up to 3 weeks after their eligible study start date.

1. ILI active surveillance participants will need to be in the emergency department for a minimum estimated time of 2 hours to complete their initial enrollment forms (90 minutes of this time is waiting for the rapid flu test result). The follow up visit for these same subjects should take an estimated time of 30 minutes.
2. Influenza positive active surveillance participants will need to be in the emergency department for a minimum estimated time of 30 minutes. The follow up visit for these same subjects should take an estimated time of 30 minutes.

3. Passive surveillance subjects are recruited via a retrospective waste sample collection process under a waiver of consent. **These subjects require no time with a research coordinator, and require no follow up visit.**

Active Surveillance:

- Enrollment
 - Screening to determine eligibility
 - Written consent
 - Enrollment questionnaire including basic demographic data, vaccination history, co-morbid illness, initial vital signs and history of present illness.
 - Collection of serum sample
 - Collection of nasopharyngeal swab sample
 - Collection of nasopharyngeal wash sample (Taiwan only)
 - Test for influenza
 - If influenza positive, then collect nasopharyngeal wash sample
- Follow up visit
 - Follow up questionnaire to assess clinical course
 - Collection of serum sample
 - Medical record review to assess clinical course

Additional influenza positive subjects:

- Enrollment
 - Screening to determine eligibility
 - Written consent
 - Enrollment questionnaire including basic demographic data, vaccination history, co-morbid illness, initial vital signs and history of present illness.
 - Collection of serum sample
 - Collection of nasopharyngeal wash sample
- Follow up visit
 - Follow up questionnaire to assess clinical course
 - Collection of serum sample
 - Medical record review to assess clinical course

Subject recruitment will occur 7 days a week, 15 hours a day so long as the university is not closed due to, but not limited to, weather.

The information that will be collected from eligible subjects includes:
Patient consent for study inclusion (See Attachments 3, 4 – Consent Form)
Patient Clinical Data Form (See Attachments 7-21 – Clinical Data Form)
Active Surveillance Forms

- 1A: Screening and Enrollment Log Active Surveillance
- 2A: Eligibility Checklist

- 3A: Subject Identification and Contact Information
- 4A: Demographic and Exposure Information
- 5A: Current Symptoms
- 6A: Medical History
- 7A: Enrollment Specimen Collection
- 8A: Follow-up Assessment
- 9A: ED Chart Review - ED Visit
- 10A: Chart Review – Inpatient Hospitalization
- 11A: Subject Withdrawal form
- 12A: Subject Checklist
- 13A: Enrollment Report
- 14A: 10% Data Accuracy Report
- 15A: QC Checklist
- 16: Specimen Quality Control Checklist

This protocol has a DMID-approved quality management plan and a DMID-approved site specific quality management plan. These approved plans outline in detail the plan for quality control and quality assurance of all data entered in our 21CFR11 compliant database, REDCap.

All data collection is the responsibility of the research coordinator and must be captured correctly, and consistent between all research coordinators across sites. The data manager, Stephen Peterson, is responsible for ensuring data integrity of his staff by the methods outlines in the quality management plan which include, but are not limited to the following:

- Quality control is the 100% real-time review of day-to-day operations, including all study-related documentation and measurement of the conduct of the protocol in real-time by delegated personnel in the field and associated centers. By front-loading quality management into the daily operations of protocol implementation with real time controls for assuring errors are detected and corrected early, unnecessary or duplicate efforts and resources are minimized, data and protocol timelines are efficiently managed. All source documents must be reviewed by the clinical team and data entry staff, for assuring accuracy and completion. QC Tools include: Form 12 (active), Form 13 (active), and Form 15 (active).
- Quality Assurance is the periodic, **retrospective**, and systematic examination of the study processes by selecting a **review frequency** and **specified sample size** (10 %), of records and key areas representing the total work effort. Research processes and systems reviewed for assurance include, *but are not limited to* determining eligibility, informed consent form and process, source data verification, study database quality control efforts, clinical laboratory processes (including processing, documenting, and shipping clinical specimens), and timely reporting of protocol deviations. Site visits conducted by a CEIRS contractor and/or DMID

may occur for the purposes of oversight of Administrative and Clinical Site performance. Issues identified from these sources should be considered toward process improvements. QA Tools include: Forms 12, 14, 15, and 16.

B.3 Methods to Maximize Response Rates and Deal with Nonresponse

Subjects are informed in detail what the study requests of them prior to enrolling the subject so the subject is made aware of all effort and benefits to them. Subjects are reminded they are in no way required to participate, and may withdraw at any moment. We do not expect a significant nonresponse rate since this is a voluntary study and subjects are compensated for their participation at enrollment and the follow up visit.

In order to maximize the collection of all data points, fully trained staff (research coordinators) who are familiar with the acute care environment will verbally ask each subject to respond to the listed structured questions in a step by-step manner. After completion of the structured clinical data form, 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. No data points will be left blank on a data collection form. If unknown or not applicable values exist, they should be marked as "999" to indicate a value does not exist. Quality assurance checks on data entry will be carried out according to our QA/QC plan which was reviewed and approved by experts from DMID. Our quality control plan allows us to estimate an 85% successful response rate. Methods to assure reliable follow-up include collection of multiple contact numbers for subjects, return phone call reminders, and flexible scheduling of return visits and/or phone follow-up calls to fit the patients' schedules within a 3 week period, A recent study for influenza shows a 92% successful response rate at the same study location.

B.4 Test of Procedures or Methods to be Undertaken

We designed the content and format for collection of samples and key data elements based on prior successful influenza studies. Those methods have been found to permit accurate and reliable collection of samples and reporting of data. The study coordinators have been directly trained by the PI and regular oversight will be provided by a Senior Coordinator (trained by the PI) to ensure consistency with procedures associated with the study.

B.5 Individuals Consulted on Statistical Aspects and Individuals Collecting and/or Analyzing Data

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Appendix
Explanation of Sample Size – Year 1

4/16/2015

The study design has 2 components:

Active surveillance and Passive surveillance.

Active surveillance requires patient recruitment and has a burden on subjects. Passive surveillance requires no patient interaction and has no time burden on patients.

Since Statement A asks for respondent time and burden we refer to our sample size as 300 per site, or 600 across sites. This includes active surveillance only.

Since Statement B asks for Sampling Methods, we refer to our sample size as 425 per site, or 850 across sites. This includes both active and passive surveillance.

Site 1 Year 1 – Johns Hopkins University

Active Surveillance Enrollment of Influenza <i>Indeterminate</i> Subjects	250
Active Surveillance Enrollment of Influenza <i>Determined</i> Subjects	50
Total Active Enrolled Subjects Per Year (Flu Season)	300
Passive Surveillance Enrollment of Subjects	125
Total Combined Active and Passive Enrolled Subjects Per Year	425

Site 2 Year 1- Chang Gung University Updated: 03/21/2011 by: MPC

Active Surveillance Enrollment of Influenza <i>Indeterminate</i> Subjects	250
Active Surveillance Enrollment of Influenza <i>Determined</i> Subjects	50
Total Active Enrolled Subjects Per Year (Flu Season)	300
Passive Surveillance Enrollment of Subjects	125
Total Combined Active and Passive Enrolled Subjects Per Year	425

Per Year (Influenza Season), Total Numbers Across Sites	
Total Active Subjects Enrolled Across Sites (Statement A)	600
Total Active and Passive Subjects Enrolled Across Sites (Statement B)	850

