Supporting Statement A for

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

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Table of contents

LIST OF ATTACHMENTS:

- ATTACHMENT 1 - Memo requesting Emergency Exemption
- ATTACHMENT 2 – Clinical Protocol #14-0076
- ATTACHMENT 3 – IRB Approval- Influenza test informed consent form, Johns Hopkins
- ATTACHMENT 4 – Informed Consent Form – Influenza Test, Chang-Gung Memorial Hospital
- ATTACHMENT 5 – Informed Consent Form – Influenza-positive individuals, Hopkins
- ATTACHMENT 6 – Informed Consent Form – Influenza-positive individuals, Chang-Gung Memorial Hospital
- ATTACHMENT 7 – Form 1A Screening and Enrollment Log Active Surveillance
- ATTACHMENT 8 – Form 2A Eligibility Checklist
- ATTACHMENT 9 – Form 3A Subject Identification
- ATTACHMENT 10 – Form 4A Demographic and Exposure Information
- ATTACHMENT 11 – Form 5A Current Symptoms
- ATTACHMENT 12 – Form 6A Medical History
- ATTACHMENT 13 – Form 7A Enrollment Specimen Collection
- ATTACHMENT 14 – Form 8A Follow-up Assessment
- ATTACHMENT 15 – Form 9A ED Chart Review
- ATTACHMENT 16 – Form 10A Chart Review – Inpatient Hospitalization
- ATTACHMENT 17 – Form 11A Subject Withdrawal Form

- ATTACHMENT 18 – Form 12A Subject Checklist
- ATTACHMENT 19 – Form 13A Enrollment Report
- ATTACHMENT 20 – Form 14A 10% Data Accuracy Report
- ATTACHMENT 21 – Form 15A QC Checklist
- ATTACHMENT 22 - Appointment Reminder Card, Johns Hopkins
- ATTACHMENT 23– Appointment Reminder Card, Chang Gung Memorial Hospital
- ATTACHMENT 24 – Manual of Operating Procedures – Johns Hopkins
- ATTACHMENT 25 – Manual of Operating Procedures – Chang Gung Memorial Hospital
- ATTACHMENT 26 – Stamped HIPAA Waiver
- ATTACHMENT 27 - 7 Day Emergency Federal Register Notice

This is a request for an emergency clearance of the "Human Influenza Surveillance of Health Care Centers in the United States and Taiwan Study" on the grounds that this is essential to the mission of The National Institute of Allergy and Infectious Diseases (NIAID) and that NIAID cannot reasonably comply with the normal clearance procedures and this would likely prevent or substantially disrupt the collection of information (5CFR 1320.13, see Attachment 1- Memo requesting Emergency Exemption). In addition, prevention of the study would cause public harm through the loss of critically needed information to understand the nature of the virus strains causing influenza during this year of increased influenza activity. The information gathered is critical for public health preparedness measures for the

next influenza season, because characterizing current influenza virus strains effects the choice of next year's influenza vaccine strains and helps determine effective treatment strategies by assessing the degree of antiviral resistance present in current influenza virus strains. The planned start date for the study March 12, 2015.

A.1 Circumstances Making the Collection of Information Necessary

The collection of the information required for the study "Human Influenza Surveillance of Health Care Centers in the United States and Taiwan" directly ties to the core mission of NIAID and NIH. The surveillance that will be conducted under this protocol (Attachment 2) will permit timely identification of Influenza viruses with pandemic potential, as well as variant seasonal influenza virus strains such as those resulting from antigenic drift; complementary clinical research will assess serologic and immunologic correlates of infection and disease severity. The sites that will be developed in the US and Taiwan will provide the US government with capacities to respond appropriately to emerging and re-emerging influenza strains. This study will provide information to better understand influenza in the human population in close to real time by utilizing advanced molecular testing methods which permit triaging (or selection) of sample for more in-depth analysis. The knowledge gained will be utilized to enhance health and reduce illness due to influenza infection.

We are currently approaching the end of an outbreak of Influenza B which, if missed, will leave us without a single surveillance sample this flu season. Additionally, we are approaching influenza season in Taiwan, a critical component of our surveillance program. If this emergency request is not approved, a full review will conclude well past the end of influenza season in both locations.

The work described in this proposal is uniquely important given that the Johns Hopkins and Taiwan research programs are one of the core new programs funded by NIAID with the expressed goal of expanded human (versus animal) surveillance and clinical research activities. This study is particularly important since the 2014-2015 dominant circulating strain is an H3N2 strain is not sensitive to the immunity induced by the influenza vaccine formulation administered to the general public. The information that will be collect through this study is necessary and will make a difference in the NIAID CEIRS program and will impact NIAID policy. If the information is not collected, program goals will not be met and program will not be completed. Since the influenza A virus season will be ending in late winter in the US and is now peaking in Taiwan, it is imperative that sample collection be initiated immediately in order to collect the needed samples.

The clinical samples and data collected through this study will be used to accomplish the following objectives:

- Rapidly identify and genetically fingerprint influenza virus strains through surveillance and molecular triaging efforts
- Perform whole genome sequencing of influenza A virus strains to identify major and minor virus quasi-species variants
- Characterize virus isolates using novel approaches designed to assess viral pathogenic fitness, antiviral resistance and relatedness to influenza vaccine strains.

- Identify biomarkers associated with severe influenza
- Serology measuring the specificity, extent and magnitude of the antibody response to infection.

Evaluation components for this project include monthly reporting to NIAID which is used for program metrics evaluation. Additionally, investigators will internally and externally (through advisory board) review and evaluate information collection, analyses and outcomes. No data have been collected or used to date.

Information collected through this study will be shared with the US and Taiwan Centers for Disease Control (CDC). The CDC serves as the national focus for developing and applying disease prevention and control, environmental health, and health promotion and health education activities designed to improve the health of the people of the United States.

The authority to collect this information is under 42 USC 285f National Institute of Allergy and Infectious Diseases (NIAID).

A.2 Purpose and Use of the Information Collection

This is a multicenter prospective observational cohort study with two surveillance components recruiting throughout the year: primarily during high rates of influenza season, but surveillance may occur during lower rates off-season as well:

For the purposes of this study, "influenza season" will begin when the site has 2 or more positive influenza samples within 7 days, and continue until there have been 3 weeks with no confirmed influenza. Surveillance may continue outside of flu season if the research may benefit from longer period of surveillance.

Active Surveillance: 600 adult subjects (18-100 years) (n=300/site) with and without influenza like illness each year, as well as subjects with laboratory confirmed influenza each year. The study population for these groups will consist of adult subjects presenting to the Johns Hopkins or Chang Gung EDs. Children, prisoners, and those unable to provide informed consent will be excluded. There are no exclusion criteria based on gender or race/ethnicity. Subjects in both of these groups will have two visits (enrollment and follow-up 3-4 weeks after enrollment).

Active surveillance will occur in the ED where individuals present for acute care. For this component, we will recruit both adults with and without symptoms of influenza like illness. Following informed written consent, eligible, consented subjects whom enrolled will complete a questionnaire detailing the demographic information, current symptoms, and past medical history. Then, we will collect a nasopharyngeal swab and serum sample from the subjects. The nasopharyngeal sample will be tested for influenza using a rapid PCR-based influenza test, and the result will be given to the subject's provider and the subject. Note: For Taiwan sites only, nasal wash will be collected from all 250 active surveillance subjects. Only NP wash samples with influenza positive confirmed cases

will be sent to the JH CEIRS Central Laboratory. Negative NP wash samples will be stored at the Linkou study site laboratory in Taoyuan County.

Three to four weeks after enrollment, all subjects will return for a follow up visit where they will give an interview to assess their clinical course and a serum sample. We will also review their medical record to further define their clinical course. All clinical information will be linked with stored nasopharyngeal and serum samples via an anonymous study ID to create a database linking samples and detailed clinical, demographic and epidemiologic information.

Active surveillance break down by recruitment groups:
500 indeterminate subjects (250/site):

- 400 symptomatic subjects (patients with influenza-like symptoms) (200/site)
- 100 asymptomatic subjects (50/site)

100 determined influenza positive subjects (50/site).

Passive Surveillance: We will perform retrospective chart review on 250 waste influenza specimens (125/site). Passive surveillance will never have direct contact with patient care and will therefore be excluded from additional comments in this supporting statement A as they are not considered to be respondents. **There is no burden to passive surveillance participants. Their samples are collected purely for clinical care and we obtain the waste samples retrospectively from the laboratory after their visit is completed.**

The data collection is an incredibly important part of this study. Negative consequences of not having this information is unintended morbidity and mortality associated with insufficient understanding of circulating influenza viruses and the factors associated with transmission, and associated medical complications. The information will be used to inform clinicians and public health experts about variant seasonal strains of influenza and the associated medical and public health related consequences.

The data collected on the influenza viruses isolated will be reviewed by program staff at NIAID/NIH. This information will be used as part of the NIAID influenza pandemic preparedness plan under the CEIRS program. Data will be used to help inform which influenza strains will be further evaluated through the risk assessment pipeline established. The data will also be shared with the US and Taiwan CDC agencies for consideration in influenza vaccine strain selection activities.

This study dovetails with other work done every year to establish the flu vaccine strains but is unique in the following way. The standard procedure for collecting influenza virus strains used to determine the following year's influenza vaccine composition involves isolating viruses in either canine kidney cells (MDCK cell lines) or in the allantoic cavity of embryonated hen's eggs. Both of these techniques can lead to the selection of virus

variants that contain mutations in their genome that are not present in the original virus strain. Our method of sequencing clinical influenza virus samples directly, then generating an influenza A virus strain from that sequence by reverse genetics allows us to capture the original virus isolate and maintain that sequence during virus isolation. Our use of primary human nasal epithelial cells is more relevant to growing these influenza virus isolates because they represent the cells the virus normally replicates in, thereby putting less "selective pressure" for variants to grow out. We will be able to test reference serum generated to influenza vaccine strains against our clinical virus strains to determine precisely how well the cross reactive immunity induced by vaccination recognizes our clinical virus isolates.

A.3 Use of Information Technology and Burden Reduction

Some patient information (that does not require explicit direct questions to patient and is otherwise available on the patient chart) described above will be collected via the Electronic Medical Record, which will reduce the burden of patient reported information.

Data will be reported and shared in an electronic format (REDCap) with the CEIRS investigators and NIAID/NIH which will reduce the paper burden.

With regard to IT systems, this work will be conducted on IT systems owned, operated and controlled outside the NIH network by non-Government entities. PIA is not required for these Systems.

In accordance with HIPAA laws, this study has been granted a waiver of consent (Attachment 26) to screen patient's medical records prior to enrollment for eligibility criteria. This will reduce the burden of the research coordinator and streamline the process for identifying eligible patients. This will also reduce the burden on the patients for patient reported information.

A.4 Efforts to Identify Duplication and Use of Similar Information

NIAID staff have searched clinical trials.org to search for similar studies. In additional, NIAID staff has consulted with the US CDC to see if there are duplicative studies. No studies to our knowledge exist that include the robust research components tied to this surveillance activity
This particular study will not duplicate other studies because of the real-time analysis and molecular triaging of samples which permits selection of samples for in–depth downstream detailed characterization, unique to this study. While influenza surveillance occurs at multiple research facilities, they are usually completed in a retrospective, downstream analysis. Our research methods will detect novel influenza strains in a more immediate manner which will trigger an immediate public health response for the

protection of those that the CDC identifies as at increased risk for complications from influenza.

A.5 Impact on Small Businesses or Other Small Entities

(Attachment 2) This protocol will not place any additional burden on the physicians. Study associated personnel will be hired and trained to provide appropriate informed consent, sample collection and data collection so that these tasks will not fall to the associated clinical staff. This protocol has been reviewed and approved by the clinical operations committee of the Johns Hopkins Hospital Emergency Department. No small entities will be impacted by this protocol.

A.6 Consequences of Collecting the Information Less Frequently

Capturing samples from this influenza season is essential for understanding the public health implications the virus may have in the future, and discerning the reasons behind the severity of the disease it causes. While some studies have demonstrated this through serological studies, our study combines serology with an analysis of the whole genome sequence of the circulating viruses, which will provide timely and critical insight into viral determinants that may be contributing to the severity of influenza and associated morbidity and mortality this season. This is the requirement for the second visit.

The information from the eligible patient participants will only be collected once therefore it cannot be collected less frequently.

A.7 Special Circumstances Relating to the Guidelines of 5 CFR 1320.5

All guidelines of 5 CFR 1320.5 are being met for this study and the project fully complies.

A.8 Comments in Response to the Federal Register Notice and Efforts to Consult Outside Agency

NIAID received approval from OMB to publish an Emergency Federal Register notice (Attachment 27), which occurred on February 26, 2015 (80 FR 10494). This allowed a 7-day comment period prior to submitting this information collection. We received one comment requesting to know if the surveys would be given to hospital employees. Our response was that the data collection would not be on the hospital employees. We received a second request for information regarding data collection plans and asking if we would be hiring any translators for English to Chinese to make traditional Mandarin versions of the instruments and data plans. NIAID responded with general information regarding the data collection plans and informed the requestor that all of the translation

requirements would be completed by investigators involved in the study. We received a third comment that was regarding the effectiveness of the influenza vaccine and the CDC. This comment did not apply to the current protocol being reviewed.

Efforts have been made to consult with persons outside of the agency to obtain their views on the protocol (Attachment 2) and data collection (Attachment 7). Agencies consulted include the US and Taiwan CDC, as well as the Biomedical Advanced Research and Development Authority (BARDA) Influenza Division within HHS.

A.9 Explanation of Any Payment of Gift to Respondents

Study participants will receive a standard nominal compensation for their time and efforts to complete the study questionnaires, return for follow up, and provide the appropriate clinical samples. The decision to provide incentive and amount provided is in keeping with standard federal and institutional guidance.

The incentive will significantly increase the likelihood of reliable data based on our research groups' extensive past experiences with similar studies. Incentive in Taiwan will be $15 for enrolling and $30 for returning for the follow up visit. Incentive for subjects in the United States will be $50 for enrolling and $75 for returning for the follow up visit. This incentive level is standard for our population for a study involving written consent and a follow up visit. The incentive difference between the sites is based on standard income differences and feedback from both sites' IRBs. These amounts have been approved by the internal IRB of the institutions and are in keeping with institutional norms for this type of investigation.

A.10 Assurance of Confidentiality Provided to Respondents

Details regarding the contractor's privacy procedures can be found in the protocol Manual of Procedures (MOP) ATTACHMENTS 24 and 25 – Protocol MOP

- Data capture will be ongoing throughout the period of the study.
- All data will be captured by fully trained research staff that have completed all required trainings by the site institution and NIAID/DMID.
- Additional laboratory updates will be entered within 30 days of the date of final laboratory result reporting.
- Data will be captured using paper DCFs and transcribed into a 21CFR11 compliant, secure, password-protected electronic database by trained study personnel.
- All data will be stored on encrypted servers and accessed via password protected, individual workstations with access logs.
- The investigators will maintain appropriate medical records and documentation related to the conduct of the research, in compliance with institutional requirements for confidentiality of subject information.

- These documents will be held at the study site in lockable cabinets under the control of the study staff and entered as coded data into a 21CRF11 compliant, secure, password-protected electronic database REDCap system.
- Clinical samples will be de-identified before analysis
- All keys identifying subjects will be destroyed at study completion
- The Privacy Act applies to the information collection per Privacy Act System of Records Notice (SORN) #09-25-0200 http://oma.od.nih.gov/ms/privacy/pa-files/0200.htm which covers clinical, basic and population-based research studies of the NIH.

A.11 Justification for Sensitive Questions

- PII will be collected initially but all data will be fully and permanently de-identified upon study completion to mitigate risk of loss of patient privacy /confidentiality.
- Data will be captured using paper DCFs and transcribed into a 21CFR11 compliant, secure, password-protected electronic database by trained study personnel.
- All data will be stored on encrypted servers accessible only via password protected, individual workstations with access logs.
- The investigators will maintain appropriate medical records and documentation related to the conduct of the research, in compliance with institutional requirements for confidentiality of subject information.
- These documents will be held at the study site in lockable cabinets under the control of the study staff and entered as coded data into a 21CRF11 compliant, secure, password-protected electronic database REDCap system.

(Attachments 3-6) Before any study procedures are performed, subjects must sign an informed consent form that complies with the requirements of 21 CFR Part 50 and 45 CFR 46 and the local IRB.
Informed consent is a process that is initiated prior to the individual's agreeing to participate in the study and continuing throughout the individual's study participation. At the time the study worker will seek informed consent, the study worker will ask the eligible candidate if he/she is literate. Subjects who are not literate are not eligible for this study.

Extensive discussion of risks and possible benefits of participation in this study, including a detailed explanation of the proposed use and disclosure of their protected health information, including specifically their specimens, will be provided to the subjects and their families before any study procedures are performed, including pre-screening of subjects for eligibility. Consent forms describing in detail the study procedures and risks are given to the subject and written documentation of informed consent is required prior to enrolling in the study and prior to performing any study procedures. Consent forms (Attachments 3-6) will be IRB approved and the subject will be asked to read and review the document. Upon reviewing the document, the

investigator will explain the research study to the subject and answer any questions that may arise. The subjects will sign the informed consent document prior to being enrolled in the study and prior to having any study procedures performed. The subjects should have the opportunity to discuss the study with their surrogates or think about it prior to agreeing to participate. By signing the informed consent form, subjects agree to complete all procedures required by this study, unless the subject withdraws voluntarily, or is withdrawn or terminated from this study for any reason. The subjects may withdraw consent at any time throughout the course of the study. A copy of the informed consent document will be given to the subjects for their records and if they refuse to take it, the study staff should document it in the subject's records. 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.

A.12 Estimates of Hour Burden Including Annualized Hourly Costs

ESTIMATES OF HOUR BURDEN – ALL SITES

Type of Respondents	Number of Respondents	Frequency of Response	Average Time per Response	Annual Hour Burden
Patients	600	1	120*/60	1200
Patients	600	1	30/60	300
Totals	600			1500

*While the initial visit time burden is reflected as 2 hours, much of this time (if not all) overlaps with the time the patient spends in the emergency department for their routine clinical care. It is our goal to minimize the amount of time that consent and sample collection take.

Note: **There is no burden on the hospital facility** as both facilities use a completely automated electronic medical record system. Electronic medical records are fully accessible by study staff and clinician investigators, who are well versed in EMR data abstraction. No pre-authorization or hospital personnel involvement is necessary for data access or abstraction.

Note: **There is no burden to passive surveillance participants.** Their samples are collected purely for clinical care and we obtain the waste samples retrospectively from the laboratory after their visit is completed.
We are recruiting a total of 600 patients who will need to be consented and have initial sample collection (n=300/site). Each patient will also have one follow up visit.

Active surveillance break-down by recruitment groups per year:
500 indeterminate subjects (250/site):

- 400 symptomatic subjects (patients with influenza-like symptoms) (200/site)
- 100 asymptomatic subjects (50/site)

100 determined flu positive subjects (50/site).

The burden was estimated by the time required to read and sign the consent form, to wait for the result of their Influenza test, and to complete the questions asked on the Data Collection Forms (Attachments 7-21). The burden in line two reflects the time required for sample collection in the follow up visit. The total hour burden is estimated at 1500 hours however the majority these hours will occur during routine patient care wait time in the emergency department for standard care.

A.12 - 2 ANNUALIZED COST TO RESPONDENTS

As listed in the Bureau of Labor Statistics, the mean hourly wage for the state of Maryland is $25.41. The Taiwan Hourly Wage is $9.10 according to their state website.

Type of Respondents	Number of Respondents	Frequency of Response	Average Time per Respondents	Hourly Wage Rate	Respondent Cost
US Patients	300	1	120/60	25.41 USD	$15,246
US Patients	300	1	30/60	25.41 USD	$7,623
Taiwan Patients	300	1	120/60	9.10 USD	$5,460
Taiwan Patients	300	1	30/60	9.10 USD	$2,730
Totals across sites	600	2	150/60		$31,059

A.13 Estimate of Other Total Annual Cost Burden to Respondents or Record Keepers

There are no additional costs to the respondents other than their time.

A.14 Annualized Cost to the Federal Government

The anticipated cost to the Federal Government is approximately $709,551 annually.

Line Item	Grade/Step	Salary	% of Effort	Fringe (if applicable)	Total Cost to Gov't
Federal Oversight					
Clinical Project Manager	GS-14	$131,053	5%		$6553
Scientific Lead/COR	GS-14	$138,136	2%		$2763
Health Specialist	GS-13	$90,823	2%		$1816
Contractor Cost					
Labor		$343,083		$99,384	$442,467
Patient Remuneration					$5,905
Materials and Supplies					$27,115
Shipping					$29,280
Indirect Costs					$145,955
Travel					$3,526
Other (IRB fees, service core fees)					$44,171

A.15 Explanation for Program Changes or Adjustments

This is a new collection of information.

A.16 Plans for Tabulation and Publication and Project Time Schedule

(Attachment 2) This protocol obtains the necessary data and samples to fulfill the objectives of many other protocols of the CEIRS network. We also will evaluate epidemiologic data from the surveillance studies from both the US and Taiwan, which will include molecular characterization and detailed sequence analysis. Data will be summarized using descriptive statistics and be published in relevant scientific journals. In addition we will assess virus virulence and replication using a relevant, model system and assess effects of virus infection on differentiated epithelial cells and repair processes integral for cellular recovery from virus infection. We will also conduct studies to assess serologic and immunologic correlates of disease and disease severity. There will be multiple scientific publications each year (at least three to four per year) resulting from the data and samples obtained.

Time schedule for the emergency project period:

March 2015 – begin data collection including sample collections

March-September 2015 – Continue data collection for the 2015 influenza season

A.16 - 1 Project Time Schedule

Activity	Time Schedule
Letters sent to respondents	1 - 2 months after OMB approval
Field questionnaire	3 - 6 months after OMB approval

A.17 Reason(s) Display of OMB Expiration Date is Inappropriate

Not Applicable

A.18 Exceptions to Certification for Paperwork Reduction Act Submissions

Not Applicable