RESEARCH PROTOCOL OF VACCINE CLINICAL TRIAL

A PHASE 2/3 DOUBLE BLINDED, RANDOMIZED, PLACEBO-CONTROLLED STUDY IN HEALTHY ADULT VOLUNTEERS IN VIETNAM TO EXAMINE THE SAFETY AND IMMUNOGENICITY OF AN INACTIVATED A/H5N1 INFLUENZA VACCINE (IVACFLU-A/H5N1) PRODUCED BY IVAC

Protocol Number: IVAC-H5N1-0203

Version Number: 2.0
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SUMMARY NAME: IVACFLU-A/H5N1 PHASE 2/3

Principal Investigator: Assoc. Prof. Tran Nhu Duong, Deputy Director, NIHE

Investigator's Institution: National Institute of Hygiene and Epidemiology, Vietnam

Sponsor: Institute of Vaccines and Medical Biologicals (IVAC), Vietnam

Manufacturer: Institute of Vaccines and Medical Biologicals (IVAC), Vietnam

Authority Agency: Ministry of Health, Vietnam

Planned time: 1st quarter 2016

Total budget: From Government budget for Science and Technology: 0 VND

From WHO: 20 billion VND

STATEMENT OF COMPLIANCE

I am Principal Investigator of the study "A Phase 2/3 Double Blinded, Randomized, Placebo-Controlled Study in Healthy Adult Volunteers in Vietnam to Examine the Safety and Immunogenicity of an Inactivated A/H5N1 Influenza Vaccine (IVACFLU-A/H5N1) Produced by IVAC." Signing below ensures that the study will be carried out on schedule, according to the content of approved protocol, and in accordance with Good Clinical Practice (GCP) as required by applicable rules of Vietnam: Decision No. 799/2008/QD-BYT, on "Guidance on Good Clinical Practice," Circular No. 03/2012/TT-BYT on "Guidance on Clinical Trial" and the Circular No. 44/2014/TT/BYT on "Medical Product Registration," Decision 1248/QD BYT on the National Guidelines on ethical issues in biomedical research; Decision 111/QD BYT on the guidelines on organizational and operational principles for IRBs; and Dispatch 6586/BYT-K2DT on the guidelines on recording/reporting SAE in clinical trial.

The study informed consent documents will embody the elements of consent as described in the Declaration of Helsinki.

All key personnel (those responsible for the design and conduct of this study) will have completed Human Subjects Protection Training prior to interaction with any participants or to have access to their confidential study data.

Hanoi, Vietnam

Principal Investigator

Tran Nhu Duong, Assoc. Prof., MD

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LIST OF ABBREVIATIONS

AE	Adverse Event
ALT	Alanine transaminase
BARDA	Biomedical Advanced Research and Development Authority
CI	Confidence Interval
Cm	Centimeter
CRF	Case Report Form
°C	Degrees Celsius
D	Day
EDTA	Ethylenediaminetetraacetic acid
EIA	Enzyme Immunoassay
EID	Egg Infectious Dose
ELISPOT	Enzyme-Linked Immunosorbent Spot
GCP	Good Clinical Practice
GMT	Geometric Mean Titer
HA	Hemagglutinin
HAI	Hemagglutination Inhibition
HBsAg	Hepatitis B Surface Antigen
HBV	Hepatitis B Virus
hCG	human Chorionic Gonadotropin
HCV	Hepatitis C Virus
ICF	Informed Consent Form
ICH	International Conference on Harmonization
ICMJE	International Committee of Medical Journal Editors
IEC	Independent Ethics Committee
IP	Investigational Product
IRB	Institutional Review Board
IVAC	Institute of Vaccines and Medical Biologicals
L	Liter
MDCK	Madin-Darby Canine Kidney
Mcg	Microgram
mL	Milliliter
Mm	Millimeter
MNT	Micro neutralization test
MOH	Ministry of Health
MOP	Manual of Procedures
N	Number (typically refers to number of subjects)
NA	Neuraminidase
NIHE	National Institute of Hygiene and Epidemiology
PI	Principal Investigator
PCR	Polymerase Chain Reaction
PBS	Phosphate buffered saline
RBC	Red Blood Cell
RNA	Ribonucleic Acid
SAE	Serious Adverse Event
SOP	Standard Operating Procedure
TCID	Tissue Culture Infectious Dose
US	United States
WBC	White Blood Cell
WHO	World Health Organization

PROTOCOL SUMMARY

Title:	A Phase 2/3 Double Blinded, Randomized, Placebo-Controlled Study in Healthy Adult Volunteers in Vietnam to Examine the Safety and Immunogenicity of an Inactivated A/H5N1 Influenza Vaccine (IVACFLU-A/H5N1) Produced by IVAC
Description of Study Design:	This is a Phase 2/3, double-blind, randomized, placebo-controlled trial to test the safety and immunogenicity of two doses given 21 days apart of the IVAC A/H5N1 vaccine. In the Phase 2 study, 300 healthy adult subjects will be randomized to receive 15 mcg of vaccine (n=100), 30 mcg of vaccine (n=100), or saline placebo (n=100). Safety and immunogenicity will be assessed in all 300 subjects. Although full evaluation of the safety will continue through Day 91, there will be an early evaluation of the safety and immunogenicity data collected through Day 43 of Phase 2 to determine whether to proceed to Phase 3 and what dose to select. A vaccine dose will be selected based on safety and immunogenicity using pre-specified criteria. The conduct of Phase 3 will be dependent on showing an HAI response titer of ≥1:40 in 60% or more vaccine recipients in at least one of the two vaccine groups in Phase 2. The dose selected from Phase 2 will be used in the Phase 3 trial. Phase 3 is a confirmatory study that will expand the safety and immunogenicity in a larger number of subjects to meet product registration in Vietnam. In Phase 3, subjects will be randomized to receive the vaccine dose selected in Phase 2 (n=1,000) or saline placebo (n=500) under double blind. Safety will be assessed in all subjects and immunogenicity will be measured in a subset of approximately 300 subjects receiving the IVACFLU-A/H5N1 (vaccinees) from 500 subjects enrolled at one of 3 study sites (Hai Phong) in Phase 3. All subjects in Phase 2 and Phase 3 will receive two injections of A/H5N1 vaccine or placebo, 21 days apart. Subjects will be male and female healthy adults from 18 through 60 years of age.
Hypothesis:	The study hypotheses are that: • Two 0.5 mL injections of whole virion monovalent A/H5N1 influenza vaccine (IVACFLU-A/H5N1) adjuvanted with alum will be safe and well tolerated in healthy adults, and • At least one of the two doses tested will be immunogenic in 60% or more of the subjects tested.

Objectives and Endpoints:	**Safety Objective in Phase 2** • To evaluate the safety and tolerability of two injections given 21 days apart of A/H5N1 vaccine at two dose levels (15 and 30 mcg).
Objectives and Endpoints:	**Safety Objective in Phase 3** • To evaluate the safety and tolerability of two injections given 21 days apart of A/H5N1 vaccine at the dose level selected from Phase 2. **Safety Endpoints for Phase 2 and Phase 3:** The safety profile of IVACFLU-A/H5N1 will be evaluated by the number and proportion of subjects experiencing AEs, related or not related, of the following five categories for all subjects, and by age group (18-40 years of age and 41-60 years age): • Number and percentage of subjects with solicited local and systemic adverse events within 30 minutes after each vaccination. • Number and percentages of subjects with solicited local adverse events (redness, swelling, pain, induration, tenderness) over a 7-day period (Days 1-7; Days 22-28) post each vaccination. • Number and percentages of subjects with solicited systemic/general adverse events (fever, fatigue/malaise, muscle aches (generalized), joint aches, chills, nausea, vomiting, headache) over a 7-day period (Days 1-7; Days 22-28) post each vaccination. • Number and percentages of subjects with unsolicited adverse events for 21 days post each vaccination. • All serious adverse events (SAEs) occurring over the entire study period (Days 1-91). **Immunogenicity Objective in Phase 2:** • To evaluate the immunogenicity of two different doses of A/H5N1 as determined by serum HAI titer ≥ 1:40 at Day 43. **Immunogenicity Objective in Phase 3:** • To evaluate the immunogenicity of the A/H5N1 influenza vaccine as determined by serum HAI titer ≥ 1:40 at Day 43 in a sample of approximately 300 subjects receiving the IVACFLU-A/H5N1 (vaccinees). **Primary Immunogenicity Endpoints Parts A and B:** • The percentage of subjects achieving an HAI titer ≥1:40 after the second vaccination on Day 43.

Objectives and Endpoints:	**Secondary Immunogenicity Endpoints: Immunogenicity Measures Will Include:** **Phase 2** • The percentage of subjects with a serum HAI titer ≥ 1:40 on Day 22. • The percentage of subjects achieving a seroresponse (at least a four-fold increase in post-vaccination titer) on Day 22 and Day 43 as determined by HAI. • The percentage of subjects with at least a four-fold rise in titer at Day 22 and 43, as determined by MN. • Geometric Mean Titer (GMT) of Day 22 and Day 43 as determined by the HAI and MN tests. • Geometric Mean Titer Ratio (GMTR) of Day 22/Day 1 and Day 43/Day 1 as determined by the HAI and MN tests. **Phase 3 (using a subset of Phase 3 subjects)*** • The percentage of subjects achieving a seroresponse (at least a four-fold increase in post-vaccination titer) on Day 43 as determined by HAI. • The percentage of subjects with at least a four-fold rise in titer at Day 43, as determined by MN*. • Geometric Mean Titer (GMT) of Day 43 as determined by the HAI and MN* tests. • Geometric Mean Titer Ratio (GMTR) of Day 43/Day 1 as determined by the HAI and MN* tests. * MN tests and associated endpoints will be conducted on Phase 3 vaccinees based on results from Phase 2 and a decision that MN testing will add value to the study.
Study Population:	Approximately 1800 healthy male and female adults, 18 to 60 years of age. Phase 2: n=300, Phase 3: n=1500.
Phase:	Phase 2 followed by Phase 3.
Number of Sites:	1 site for Phase 2; 3 sites for Phase 3
Study Duration:	Approximately 30 months (including approximately a 8-10 month break for evaluation of initial cohort; and about 10 months for data analysis, completion of clinincal study report and result approval by local IRB and regulatory).
Participation Duration:	Approximately 3 months for each subject, excluding screening.
Description of Agent or Intervention:	Monovalent A/H5N1 influenza vaccine (MIV), whole virion inactivated, purified by sucrose gradient on ultracentrifuge (IVAC,

	Nha Trang, Vietnam), or placebo (IVAC, Nha Trang, Vietnam). The vaccine will be produced in eggs, inactivated with formaldehyde, and formulated with aluminum hydroxide 0.6 mg/0.5 mL with no preservative.
Estimated Time to Complete Enrollment:	Full enrollment in the Phase 2 part of the study is anticipated within 2-4 weeks of first injection. Full enrollment in the Phase 3 part of the study is anticipated to be within 2-4 weeks for each site.

Table 1: Trial Scheme - Schedule of Events for Phase 2 Participants

Study Activities	S1 (-30 to -3 days before D1)	Study Day (in number of days from day of administration of Injection 1 or D1)									
		S2/D1	D2 to D7	D8	D9 to D21	D22	D23 to D28	D29	D30 to D42	D43	D91
Information process and written informed consent	X (ICF A)	X (ICF B)									
Collect baseline demographic data	X										
Collect/review medical history	X	X				X					
Perform general physical examination	X										
Perform targeted physical examination		X		X		X		X		X	
Collect serum and whole blood for screening clinical laboratory tests	X										
Collect serum for HBV and HCV testing	X										
Perform urine pregnancy check (fertile women)	X	X				X					
Collect serum and whole blood for clinical safety laboratory tests				X		X		X			
Check/confirm inclusion/exclusion criteria	X	X				X					
Randomization		X									
Collect serum for influenza A/H5N1 serology (pre-vaccination on days of study vaccination; 21 days post 2nd dose)		X				X				X	
Administer study vaccine or placebo		X				X					
Observe for immediate reactions for 30 minutes		X				X					
Instruct participant on use of Diary Card		X				X					
Participant completes the Diary Card		X	X			X	X				
Study staff check on subject's well-being and Diary Card completion			Visit D2; Visit/Call D6				Visit/Call D23 & D27				Call
Review and collect Diary Card				X				X			
Review interim AEs/SAEs				X		X		X		X	X (SAEs only)
Report SAEs to sponsor, and regulatory authorities, as required		X	X	X	X	X	X	X	X	X	X
Subject completion of study											X

Table 2: Trial Scheme - Schedule of events for Phase 3 participants

Study Activities	S1/D1 (-4 before D1 or on D1)	Study Day (in number of days from day of administration of Injection 1 or D1)								
		D2 to D7	D8	D9 to D21	D22	D23 to D28	D29	D30 to D42	D43	D91
Information process and written informed consent	X									
Collect baseline demographic data	X									
Collect/review medical history	X				X					
Perform general physical examination	X									
Perform targeted physical examination	X*		X		X		X		X	
Perform urine pregnancy check (women)	X**				X					
Check/confirm inclusion/exclusion criteria	X**				X					
Randomization	X									
Collect serum for influenza A/H5N1 serology (pre-vaccination on days of study vaccination) [1]	X								X	
Administer study product (vaccine or placebo)	X				X					
Observe for immediate reactions for 30 minutes	X				X					
Instruct participant on use of Diary Card	X				X					
Participant completes the Diary Card	X	X			X	X	-			
Study staff check on subject's well-being and Diary Card completion		Visit/Call D2 & D6				Visit/Call D23 & D27				Call
Review and collect Diary Card			X				X			
Review interim AEs/SAEs			X		X		X		X	X (SAEs only)
Report SAEs to sponsor, and regulatory authorities, as required	X	X	X	X	X	X	X	X	X	X
Subject completion of study										X
*Perform only if D1 is separate from S1; ** Perform on S1 and repeat only if D1 is separate from S1 Interval between S1 and D1 can be up to 4 days										

1. In Phase 3 sera for influenza serology will be collected at one of the three specified clinical sites.

Table 3: Summary of Study Design for Phase 2 and B

PHASE 2		
Study group	Description of Intervention	Number of subjects
Low dose group	15 mcg HA/0.5 ml vaccine	100
High dose group	30 mcg HA/0.5 ml vaccine	100
Placebo group	Placebo (PBS)	100
Total		300

An early evaluation of immunogenicity/safety through Day 43 of Phase 2 and decision (with dose selection) to proceed to Phase 3.

PHASE 3		
Study group	Description of Intervention	Number of subjects
Vaccine group	Dose Selected from Phase 2	1000
Placebo group	Placebo (PBS)	500
Total		1500

RESEARCH PROTOCOL

1 Key Roles for Individuals and Institutions Involved

Principal Investigator:	Assoc. Prof. Tran Nhu Duong Deputy Director, NIHE
Sub-Investigator	Vu Dinh Thiem, PhD, MD Head of Epidemiology Department, NIHE
Investigator's Institution:	National Institute of Hygiene and Epidemiology (NIHE)
Institutional Review Boards:	NIHE IRB; WHO ERC and EC, MOH, Vietnam
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Sponsor	Institute of Vaccines and Medical Biologicals (IVAC) 9 Pasteur, Nha Trang, Vietnam Contact: Le Van Be, MD, PhD, Director phone: (+84 90) 3501529 fax: (+84 58) 3823815 email: ivaclevabe@dng.vnn.vn or ivaclevanbe@gmail.com
Study Monitoring Organization:	FHI 360 (U.S. and Vietnam offices)
Clinical Site, Phase 2	Khanh Hoa Provincial Health Department (data entry, CRF storage). Recruitment, consent, blood draws, vaccinations and follow-up visits will happen at the Ninh Da, Ninh Binh and Ninh Quang Communes.
Clinical Sites, Phase 3	1. Khanh Hoa Provincial Health Department (data entry, CRF storage), with study activities at the Ninh Da, Ninh Binh, and Ninh Quang Commune Health Centers. 2. Hai Phong Provincial Preventive Medicine Center (data entry; CRF storage), with study activities at the Cap Tien, Kien Thiet, and Hung Thang Commune Health Centers. 3. Hoa Binh Provincial Preventive Medicine Center (data entry; CRF storage), with study activities at the Hop Kim, Nam Thuong, and Thuong Bi Commune Health Centers.
Clinical and Specialty Laboratories:	Nha Trang Pasteur Institute (Central Clinical laboratory) for Phase 2 and National Institute of Hygiene and Epidemiology (NIHE) (for immunogenicity testing).

Sponsor Medical Monitor:	Vien Chinh Chien, MD, PhD Vice Director, Institute of Vaccines and Medical Biologicals (IVAC) 09 Pasteur Str., Nha Trang City, Khanh Hoa province - VIET NAM Tel 84 058 3822408 MoB: 0914059557 Email:chienvc66@yahoo.com
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2 Background Information and Scientific Rationale

2.1 Background Information

2.1.1 Overview of Influenza Disease

Influenza is one of the major infectious disease threats to the human population due to both the adverse health impact of annual influenza epidemics and the detrimental global consequences of influenza pandemics. The recent A/H1N1 (2009) pandemic and the extensive dissemination of the influenza A/H5N1 virus in bird populations with ongoing zoonotic transmission to humans illustrate the unpredictability of the influenza virus. The effects of an influenza pandemic are likely to be greatest in resource-limited countries where individuals may be more susceptible to severe outcomes of influenza due to underlying nutritional deficiencies and concomitant illness, limited access to health care, and the lack of widespread use of vaccines against common causes of bacterial pneumonia. As demonstrated by the recent influenza A/H1N1 pandemic outbreak, vaccine supplies were limited so that vaccine availability in developing countries was delayed or unavailable. The WHO began the Global Action Plan (GAP) in 2006 to address the issue of influenza vaccine shortfall. The program addressed the global shortage of influenza vaccines by 1) increasing seasonal vaccine use, 2) increasing vaccine production capacity, particularly in low income countries, and 3) pursuing research and development for better vaccines. As part of the second objective, GAP has supported the production of influenza vaccine in 14 countries. IVAC joined the GAP program in 2007.

Although the A/H1N1 (2009) pandemic has subsided and the virus has become endemic, the threat of another pandemic due to avian influenza A/H5N1 remains constant. Since 1997, highly pathogenic A/H5N1 avian viruses have caused both widespread outbreaks in poultry with high mortality and sporadic, severe, and fatal disease in humans. Southeast Asian countries, including Vietnam, have been affected by influenza A/H5N1. From 2003 through March 2015, 826 confirmed human cases of A/H5N1 influenza infection have been reported by the World Health Organization; including 440 fatal cases.[1] Southeast Asian countries accounted for 42% of all confirmed influenza A/H5N1 cases reported since 2003, and influenza A/H5N1 infection in animals is now thought to be endemic in the region.[2] As of March 2015, Vietnam has reported 127 confirmed human cases and 64 deaths. In 2014, 2 cases of A/H5N1 avian influenza were reported in Vietnam. Therefore, the risk of transmission to human is still present.

Currently, no influenza A/H5N1 vaccine has been licensed in Vietnam. If a pandemic emerged, vaccine demand could be huge. In Vietnam there are two influenza vaccine manufacturers, VABIOTECH and

IVAC. VABIOTECH made a small GMP lot of H5 influenza vaccine and completed a Phase 3 clinical trial. IVAC recently completed its first GMP production and has completed a Phase 1 clinical trial for H5N1 vaccine among healthy adults in Vietnam. There is also a need for development of seasonal influenza vaccines. IVAC has been proactive in development and production of flu A/H1N1, A/H5N1, A/H7N9, and seasonal flu vaccines under the guidance from the MOH.

2.1.2 Treatment and Prevention (Vaccine, Biological)

Manufacturers have developed various whole virus influenza vaccines with and without adjuvant against A/H5N1 and tested these candidates in many trials in healthy adults. For A/H5N1 candidates used in clinical trials, HA content has ranged from 1.25 mcg to 45 mcg. Egg-based whole virus A/H5N1 vaccines licensed for use in adults all include alum adjuvant and have HA content ranging from 6 to 30 mcg; all but one vaccine are licensed in a two-dose regime. Mild pain at the injection site and headache were the most common adverse reactions identified with various candidates. Vaccines were well tolerated, but injection site discomfort was more frequent among those receiving candidates containing alum.[3,4,5,6,7,8,9]

The WHO Global Action Plan is an initiative to support development of new influenza vaccines, increase demand for seasonal vaccines, and enhance influenza vaccine production capacity.[10] With support from international donors, including the US Department of Health and Human Services, WHO leads a program to support influenza vaccine manufacturers in developing countries that is crucial to increasing overall manufacturing capacity as well as to enhancing regional access to vaccines. In the first phase of the plan, WHO provided funding and assistance to manufacturers in six countries, including Vietnam, to establish influenza vaccine production capacity.

2.1.3 Summary Results of Related Preclinical Trials and Clinical Trials

The Institute of Vaccines and Medical Biologicals (IVAC) in Vietnam has been working with WHO since 2006, and in January 2011 IVAC also began to work with PATH and expert consultants to produce a prototype pandemic influenza vaccine. IVAC received technology and funding through WHO to build the production line of influenza vaccine, under GMP-WHO standards, with the potential for expansion to > 3 million doses per year and the reliable egg supply established for influenza vaccine manufacturing in place. With the chicken farm controlled and under biosecurity standards, IVAC has successfully developed the “core” process to produce whole virion, formalin inactivated, purified influenza vaccine to proactively and quickly response to new virus variant which can cause epidemic or pandemic. When cost, technical complexity, and immunogenicity were considered, IVAC decided to pursue development of a whole virus pre-pandemic A/H5N1 influenza vaccine, which would be tested with and without aluminum hydroxide (alum). During this time, however, there was an intervening influenza A/H1N1 pandemic. This pandemic, in addition to the reduced difficulty of manufacturing A/H1N1 vaccines (as compared to A/H5N1) led IVAC to proceed with developing a monovalent A/H1N1 vaccine instead of the A/H5N1. IVAC was able to establish the manufacturing process according to Good Manufacturing Practice (GMP) and to demonstrate clinical safety of a monovalent product by testing according to Good Clinical Practice (GCP).

The monovalent whole virion non-adjuvanted A/H1N1 vaccine was successfully manufactured, tested, and released by IVAC. Subsequent clinical evaluation during Phase 1 study conducted at Pasteur Institute

Ho Chi Minh City (PI-HCMC) in 2012 demonstrated that two administrations of this unadjuvanted vaccine were safe and well tolerated, and highly immunogenic when administered at a dose of 15 mcg. Given the success of early development of A/H1N1/09 vaccine, IVAC is moving forward with original plans to conduct clinical evaluation of pandemic A/H5N1 vaccine. However, taking into account that immunogenicity of A/H5N1 vaccine is likely to be less robust than that of A/H1N1 vaccine, the vaccine in this study is formulated with an adjuvant – aluminum hydroxide. The adjuvant is intended to serve two purposes – to improve immunogenicity of A/H5N1 vaccine and to provide a dose-sparing effect. Preclinical evaluation of alum-adjuvanted A/H5N1 vaccine demonstrated its good antigenicity in a mouse study, protective capacity against a lethal A/H5N1 challenge in a ferret model, and an acceptable safety profile in a rabbit toxicology study.

A clinical trial of IVAC's A1/H5N1 vaccine conducted in 75 subjects at the Ben Luc Health District in Vietnam in 2014 showed that the IVAC's A/H5N1 vaccine is safe and immunogenic at doses of 7.5 and 15 mcg.

Safety Results of IVAC's Phase 1 A/H5N1 Vaccine in Vietnam: The A/H5N1 vaccine was safe and well tolerated at both the 7.5 mcg and 15 mcg dose. The results are presented in Tables 4-6. The following observations were made regarding safety of the A/H5N1 vaccine:

- There were no SAEs in the study, either related or not related to the vaccine.
- There was no immediate (within 60 minute) reactogenicity reported with either dose of the vaccine or placebo.
- None of the study subjects discontinued study participation because of an AE.
- All solicited local reactogenicity, after the first and second doses of both the low and high dose of the vaccine, was reported to be mild.
- The high dose vaccine group reported a slightly greater number of solicited systemic reactogenicity with slightly more moderate severity, after both doses of vaccine, than either the low dose or placebo groups.

Table 4. Summary of Demographic and Baseline Characteristics

	Dose, 7.5 mcg n=31 n, (%)	Dose, 15 mcg n=32 n, (%)	Placebo n=12 n, (%)
Sex			
Male	20 (65)	19 (59)	5 (42)
Female	11 (35)	13 (41)	7 (58)
Age (years)			
Mean	23.7	23.5	23.7
Range	19-30	19-30	18-28

Table 5. Summary of All Solicited Adverse Events Occurring after 60 Minutes through 7-days after 1st and 2nd Vaccination Combined

Solicited event	Dose, 7.5 mcg N = 31		Dose, 15 mcg N = 32		Placebo N = 12	
	n	%	n	%	n	%
Subjects with at least one solicited AE	26	83.9	26	81.3	4	33.3
Subjects with at least one local event	25	80.6	24	75	3	25
Pain when touching injection site	21	67.7	23	71.9	3	25
Painful feeling after injection	18	58.1	16	50	1	8.3
Subjects with systemic event	13	41.9	14	43.8	4	33.3
Chills	1	3.2	3	9.4	0	0
Cough	3	9.7	2	6.3	2	16.7
Fatigue/Malaise	3	9.7	5	15.6	2	16.7
Fever (Through temperature)	0	0	3	9.4	0	0
Sore Throat	2	6.5	2	6.3	2	16.7

From CSR Table 14.3.2.1.1
Notes:
1. N– Total number of subjects who received at least one vaccine dose; n – Total number of subjects meeting the event.
2. Percentages are based on the total number of subjects in the vaccine group (N).
3. All solicited AEs occurring greater than 60 minutes after administration of any dose of study product through 7 days (Days 0-6) following any dose are considered.
4. Subjects experiencing multiple events within the same term are counted only once under those categories.
5. *95% confidence interval for single proportion is calculated using Exact Clopper-Pearsen method.

Table 6. Participants Reporting Any Unsolicited AE by Grade, System/Organ/Class & Preferred Term & Treatment Group

System/Organ/Class (Preferred Term)	Low Dose (N=31)	High Dose (N=32)	Placebo (N=12)
Number of subjects with at least one AE	12 (39%)	12 (38%)	4 (33%)
Injury (Clavicle fracture)	1*	0	0
Investigations (Alanine aminotransferase increased)	1	1	0
Investigations (Bilirubin increased)	3	0	0
Gastrointestinal (apthous stomatitis)	0	1	0
Gastrointestinal (nausea)	0	1	0
Immune system (food allergy)	0	0	1
Injury (Soft tissue injury)	0	1	0
Infection (Urinary tract infection)	0	0	1
Investigations (Heart rate increased)	1	0	0
Nervous System (Dizziness)	0	1	0
Nervous System (Dizziness postural)	1	0	0

Psychiatric (Anxiety)	1	0	0

Table 6, continued

System/Organ/Class (Preferred Term)	Low Dose (N=31)	High Dose (N=32)	Placebo (N=12)
Psychiatric (Depressed mood)	1	0	0
Reproductive System (Dysmenorrhea)	0	1	0
Skin and Subcutaneous Tissue Disorder (Discoloration)	1	0	0
Skin and Subcutaneous Tissue Disorder (Pruritus)	0	0	1

14 AEs were mild, 4 moderate and 1* severe

Safety Summary

- The percentage of reported unsolicited adverse events was similar for vaccine (low dose) 39%, vaccine high dose (38%) and placebo participants (33%).
- Almost all unsolicited AEs were reported as mild to moderate in severity. Only 1 unsolicited AE was reported as severe (clavicle fracture (unrelated); low dose vaccine group).
- Unsolicited AEs deemed related to the vaccine included nausea (mild), increased bilirubin (moderate), increased alanine aminotransferase (moderate), and dizziness (mild).

Immunogenicity Results of IVAC's Phase 1 A/H5N1 Vaccine in Vietnam

Immunogenicity responses to each dose (7.5 and 15 mcg) of vaccine were measured on Day 21 after each vaccination. All study subjects were sero-negative (HAI and MNT < 1:10) prior to vaccination. The proportion of subjects achieving an HAI titer ≥ 1:40 after each dose and those achieving a ≥ 4-fold rise in HAI titer is presented in **Table 7. Table 8** summarizes the geometric mean titer and geometric mean fold ratio at baseline and 21 days after each vaccination for HAI titers. Similar summaries were performed for the serum neutralizing antibodies in **Tables 9 and 10**, presenting the proportion of subjects with a titer ≥ 1:40 after each dose, and summarizing the geometric mean and geometric mean fold rise for neutralizing antibodies, respectively.

Serum Hemagglutination Inhibition (HAI) Antibodies: Seven (22.6%) subjects from low dose vaccine and 9 (28.1%) subjects from high dose vaccine achieved an HAI titer ≥1:40 after vaccination 1. The number of subjects achieving the HAI titer ≥1:40 after vaccination 2 increased to 13 (41.9%) and 18 (56.3%) subjects for low dose vaccine and high dose vaccine, respectively. No placebo subjects reported HAI titer ≥1:40 at any visit. There was a significant difference in response rates from placebo after dose 1 for high dose vaccine (95% CI: 0.82, 45.37) only and after dose 2 for low dose vaccine (95% CI: 13.14, 59.23), high dose vaccine (95% CI: 26.68, 71.83), and the combined vaccine group (95% CI: 22.18, 61.24). There was no significant difference (i.e., the lower bound of the 95% CI for the rate difference >0) between the response rates of low dose and high dose vaccine after either dose (Dose 1 95% CI: -15.78, 26.10; Dose 2 95% CI: -9.89, 36.31).

Table 7. **Hemagglutination Inhibition (HAI) immune response (titer ≥1:40) rates after two doses of vaccine measured on Day 0, 21, and 42**

Dose	No. of	Number (%) with HAI Titer ≥ 40		
group	subjects	Day 0	Day 21	Day 42
High dose	32	0	9 (28.1)	18 (56.3)
Low dose	31	0	7 (22.6)	13 (41.9)
Combined	63	0	16 (25.4)	31 (49.2)
Placebo	12	0	0	0

A four-fold rise was observed from baseline to post first vaccination in 11 (35.5%) and 12 (37.5%) subjects for low dose vaccine and high dose vaccine, respectively. The number of subjects reporting a 4-fold rise increased from baseline to post-vaccination 2 with 21 (67.7%) and 23 (71.9%) subjects responding in low dose vaccine and high dose vaccine, respectively. However, not all vaccinees with a 4-fold rise reached a titer of 1:40 (**Table 7**) because titers rising from baseline (1:5) to 1:20 were considered a 4-fold rise. Twenty (31.7%) subjects had a 4-fold rise between post-vaccination 1 and post-vaccination 2 with 9 (29.0%) subjects in low dose vaccine and 11 (34.4%) subjects in high dose vaccine. All 95% CIs at each time point showed a significant difference from placebo, but a significant difference was not observed between low dose vaccine and high dose vaccine at any time point.

The GMT's and GMFR's in the vaccine groups were significantly higher (i.e., the lower bound of the 95% CI for the GMT/GMFR ratio >1.0) than placebo, but there was not a difference in GMT's or GMFR's between the low dose vaccine and high dose vaccine group at either dose (**Table 8**).

Similar to the seroconversion rates, there was no difference in the GMTs according to dose. In the combined high and low dose vaccine groups the GMT was 12.3 after one dose and 25.8 after two doses. The mean fold rise in the combined vaccine group was 5.2.

Table 8: **Geometric mean HAI titers after first dose on Day 21 and after the second dose on Day 42**

Dose	No. of subjects	Day 0	Day 21	Day 42	HI fold increase after 2 doses
High dose	32	5.0	11.9	27.1	5.4
Low dose	31	5.0	12.8	24.5	4.9
Combined	63	5.0	12.3	25.8	5.2
Placebo	12	5.0	5.0	5.0	1.0

Serum Neutralizing Antibodies (Microneutralization): Four (12.9%) subjects from low dose vaccine and 6 (18.1%) subjects from high dose vaccine achieved an MNT titer ≥1:40 after vaccination 1. The number of subjects achieving the MNT titer ≥1:40 after vaccination 2 increased to 11 (35.5%) and 13 (40.6%) subjects for low dose vaccine and high dose vaccine, respectively. No placebo subjects reported MNT titer ≥1:40 at any visit.

Table 9. **Neutralizing Antibody Titer (MNT) immune response (titer ≥1:40) rates after two doses of vaccine measured on Day 0, 21, and 42**

Dose	No. of	Number (%) with MNT titer ≥ 40		
group	subjects	Day 0	Day 21	Day 42
High dose	32	0	6 (18.1)	13 (40.6)
Low dose	31	0	4 (12.9)	11 (35.5)
Combined	63	0	10 (15.8)	24 (38.1)
Placebo	12	0	0	0

A similar trend was observed in the GMT's and GMFR's with a significantly higher result in the vaccine group than the placebo group post vaccination 2 (**Table 4**). A higher percentage of subjects with elevated neutralizing antibodies are observed post vaccination 2 when compared to post vaccination 1 for both low dose vaccine and high dose vaccine.

Table 10: **Geometric mean MNT titers after first dose on Day 21 and after the second dose on Day 42**

Dose	No. of subjects	Day 0	Day 21	Day 42	MNT fold increase after 2 doses
High dose	32	5.0	9.4	23.3	4.65
Low dose	31	5.0	9.4	21.9	4.37
Combined	63	5.0	9.4	22.6	4.51
Placebo	12	5.0	5.0	5.0	1

The rate of responses to vaccination with H5N1 is summarized in Table 8. The following conclusions can be drawn:

- About 25% subjects exhibited seroresponses to the first vaccine dose and 50% responded after the second dose.
- Immune responses to the high dose (15 mcg) were higher than those to the low dose (7.5 mcg), but the difference was not significant.
- Seroresponses, as defined by a post-dose 2 HAI titer of ≥40, were observed in 41.9% (13/31) of low dose recipients and 56.3% (18/32) of high dose recipients.
- Seroresponses ≥ 4-fold rise post-dose 2 were observed in 67.7% (21/31) for low dose and 71.9% (23/32) for high dose recipients.

These results suggest that the IVAC vaccine at the doses tested will not meet the stringent FDA/EMA pandemic vaccine criterion for licensure. Thus, this current trial is being conducted to evaluate the safety and immunogenicity of a higher vaccine dose (30 mcg). Note however, that other similar vaccines of the same or lower immunogenicity have been licensed by various National Regulatory Authorities (NRA) elsewhere.

Appendix A presents immunogenicity data from trials of 30 different alum-adjuvanted H5N1 vaccines administered intramuscularly to adults. The following conclusions may be taken from these studies: 1) vaccine immunogenicity (with or without adjuvant) is clearly lower than that generated with H1N1

vaccines, 2) vaccine doses under 7.5 mcg, adjuvanted or not, induced lower response levels, 3) doubling or tripling the dose from 5-7.5 mcg to 15 mcg had a clear benefit, and 4) in some cases 30 mcg showed to be an optimal dose to use.

2.2 Dose Rationale

Vaccination schedules have varied in clinical trials of A/H5N1 candidate whole and split or subunit inactivated influenza vaccines. Since populations are immunologically naïve to pandemic strains, studies conducted in adults have used a two-dose intramuscular vaccination schedule. The manufacturers who specifically tested whole virion influenza A/H5N1 vaccines can be found in the table in Appendix A. After consultation with a Product Development Advisory Group including members from the WHO, IVAC, PATH, Biomedical Advanced Research and Development Authority, and independent consultants who are expert in influenza vaccine development, IVAC selected to initially evaluate two dose levels of vaccine (7.5 and 15 mcg HA content) per 0.5 mL dose given 21 days apart in its Phase 1 study. This was based on experience of other manufacturers who developed whole virion based A/H5N1 vaccine. However, the results of our Phase 1 study suggest that we may not have yet reached an optimal dose. Phase 2 of this study is designed to evaluate the safety the 30 mcg dose and compare its immunogenicity with the 15 mcg dose. Successful identification of a dose will lead to Phase 3, in which the selected dose will be further evaluated for safety and immunogenicity.

All but one vaccine developed so far against avian H5N1 virus required use of an adjuvant to achieve reasonable levels of immunogenicity. For the inactivated split or subunit vaccine manufacturers such as Sanofi-Aventis, GlaxoSmithKline, CSL, and Novartis, the 15 mcg HA/0.5 mL per injection is standard for seasonal trivalent influenza vaccines, although higher and lower doses have been tested in clinical trials. See Appendix A for a WHO summary of clinical trials of A/H5N1 vaccines.

2.3 Potential Risks and Benefits of the A/H5N1 Inactivated Vaccine

All potential risks and known benefits are detailed below and will be provided and explained to study subjects. Before participating in the study, subjects will be given the information sheet to read and will be invited to attend a meeting to learn more about the trial. During the study, if there are any changes related to the research plan or related to the product that may affect the subject's decision to continue participating in the study, the subject will be notified in writing of such information.

Potential Risks to Participant Well-Being

Administration of study product may cause the subject immediate, mild pain in the arm. The study vaccine to be used for this trial is produced using similar methods as is seasonal trivalent inactivated influenza vaccine currently approved for use in Vietnam and other countries; therefore, side effects may be similar. These may include pain and inflammation at the injection site or systemic symptoms such as fever and body aches. However, serious or allergic reactions may also be possible.

Pain after injection and tenderness (painful when touched) were the only local reactions reported by the 63 vaccine recipients in the Phase 1 A/H5N1 study. Pain was reported by 53.9% of vaccine recipients and tenderness was reported by 69.8% of vaccine recipients.

For systemic reactions, headache was most commonly reported both by vaccine recipients (20.6%) and placebo recipients (33.3%). This category also had the highest report of moderate severity (3 of the 13, or 23%), with no moderate reports in the placebo group.

Because they occurred within 7 days of injection, the reactions listed below are regarded as related to the vaccine, in order of most frequently reported:

- Tenderness
- Pain
- Headache
- Cough
- Fatigue/Malaise
- Feeling Feverish
- Chills
- Fever

Unsolicited AEs deemed related to the vaccine included short-lived nausea (mild), increased bilirubin (moderate), increased alanine aminotransferase (moderate), and dizziness (mild).

These potential risks are addressed by several measures:

- Monitoring of subjects closely for 30 minutes after vaccination and providing emergency care for any immediate reactions.
- Monitoring of subjects for adverse events which are not life-threatening and providing care for these at nearby local hospitals.
- Monitoring of subjects for severe adverse events and providing care for these at nearby local hospitals.

During the study period if a serious adverse event occurs, IVAC will ensure coverage for the full cost of treatment according to the laws of Vietnam for research participants.

2.3.1 Known Potential Benefits

Potential subjects will have aspects of their health status screened by qualified clinicians and through laboratory testing. This screening will be free of cost to the subject and may provide important health information to the screening candidates. Screening laboratory tests will be offered to all people who present for screening (Phase 2 only), even those who may screen out based on medical history and physical exam. Results will be reviewed with them and shared with their personal physician, if so desired by the participant.

Protection from A/H5N1 influenza is a possible benefit, although because the vaccine is experimental it cannot be guaranteed. Subjects may not benefit personally through study participation. By participating in

this study, subjects will contribute information on the safety and immunogenicity of this new vaccine against influenza in Vietnam. Development of new influenza vaccines, such as this IVACFLU-A/H5N1, that are locally produced and potentially less expensive, would be a significant contribution to public health in Vietnam and regionally.

There are no other known potential benefits to the subject for participation in this trial. Given the history of good safety profiles of influenza vaccines, the risk-benefit ratio is considered favorable, especially considering that all subjects will be under the observation of qualified medical personnel.

3 Study Objectives and Outcome Measures

3.1 Study Objectives

3.1.1 Safety Objective in Phase 2

- To evaluate the safety and tolerability of two injections given 21 days apart of A/H5N1 vaccine at two dose levels (15 and 30 mcg).

3.1.2 Safety Objective in Phase 3

- To evaluate the safety and tolerability of two injections given 21 days apart of A/H5N1 vaccine at the dose level selected from Phase 2.

3.1.3 Primary Immunogenicity Objective in Phase 2

- To evaluate the immunogenicity of two different doses (15 mcg and 30 mcg) of A/H5N1.

3.1.4 Primary Immunogenicity Objective in Phase 3

- To evaluate the immunogenicity of the A/H5N1 influenza vaccine in a sample of approximately 300 subjects receiving the IVACFLU-A/H5N1 (vaccinees).

3.2 Outcome Measures

3.2.1 Primary and Secondary Immunogenicity Endpoints

Primary Immunogenicity Endpoints (Phase 2 and Phase 3): Immunogenicity Measures will Include:

- Percentage of subjects achieving an HAI titer ≥1:40 after the second vaccination on Day 43.

[Note: this endpoint is equivalent to another commonly used endpoint of seroconversion as defined as prevaccination titer <1:10 and a post-vaccination titer ≥1:40 OR significant increase in antibody titer (a

pre-vaccination titer of ≥1:10 and at least a four-fold increase in post-vaccination titer), since all subjects are expected to have baseline titer of < 1:10.]

Dose Selection Criteria for Phase 3: The higher vaccine dose tested (30 mcg) will be selected if it induces higher immune responses than the lower dose as described in the table below. Other factors such as safety and manufacturing costs will also be considered.

Dose	Percentage of subjects with HAI ≥ 40 after two vaccinations			
Low dose (15 mcg)	< 60%	60-64%	65-74%	≥ 75%
High dose (30 mcg)	≥ 60	> 15 mcg dose	> 13% higher	Any
Dose selection	30 mcg	30 mcg	15 mcg, if Δ <13%	15 mcg
			30 mcg if Δ ≥13%	

Note Δ represent a difference in HAI in the high and low dose groups.

Success Criterion for Phase 3: the selected dose of vaccine induces responses in 60% or more of the approximately 300 subjects receiving the IVACFLU-A/H5N1 (vaccinees) selected for HAI immunogenicity testing.

Secondary Immunogenicity Endpoints: Immunogenicity Measures will Include:

Phase 2 (HAI and MN testing in all 300 Phase 2 subjects)

- Percentage of subjects with a serum HAI titer ≥ 1:40 at Day 22.
- Percentage of subjects demonstrating an HAI seroresponse of at least a four-fold increase in post-vaccination titer on Day 22 and Day 43.
- Percentage of subjects with at least a four-fold rise in titer at Day 22 and Day 43, as determined by microneutralization (MN).
- Geometric Mean Titer (GMT) of Day 22 and Day 43 as determined by the HAI and MN tests.
- Geometric Mean Titer Ratio (GMTR) of Day 22/Day 1 and Day 43/Day 1 as determined by the HAI and MN tests.

Phase 3 [HAI testing in approximately 300 subjects receiving the IVACFLU-A/H5N1 (vaccinees); MN testing to be determined based on the results from Phase 2]

- Percentage of subjects demonstrating an HAI seroresponse of at least a four-fold increase in post-vaccination titer on Day 43.
- Percentage of subjects with at least a four-fold rise in titer at Day 43, as determined by microneutralization (MN)*. (Only a subset of Phase 3 subjects will be tested for MN.)
- Geometric Mean Titer (GMT) of Day 43 as determined by the HAI and MN* tests.
- Geometric Mean Titer Ratio (GMTR) of Day 43/Day 1 as determined by the HAI and MN* tests.

* MN tests and associated endpoints will be conducted on Phase 3 vaccinees based on results from Phase 2 and a decision that MN testing will add value to the study.

3.2.2 Safety Endpoints

The safety profile of IVACFLU-A/H5N1 will be evaluated by the proportion of subjects experiencing AEs, related or not related, of the following five categories for all subjects and by age group (18-40 years of age and 41-60 years age):

- Number and percentage of subjects with solicited local and systemic adverse events within 30 minutes after each vaccination.
- Number and percentages of subjects with solicited local adverse events (redness, swelling, pain, induration, and tenderness) over a 7-day period (Days 1-7; Days 22-28) post each vaccination.
- Number and percentages of subjects with solicited systemic/general adverse events (fever, fatigue/malaise, muscle aches (generalized), joint aches, chills, nausea, vomiting, and headache) over a 7-day period (Days 1-7; Days 22-28) post each vaccination.
- Number and percentages of subjects with unsolicited adverse events for 21 days post each vaccination.
- All serious adverse events (SAEs) occurring over the entire study period. (Days 1-91).

4 Study Design

4.1 Study Design

This is a Phase 2/3, double blinded, randomized, placebo-controlled study. The trial will be conducted in two stages: Phase 2 will enroll approximately 300 healthy male and female adults, 18 to 60 years of age. The subjects will be randomized to one of the three treatment groups at a 1:1:1 ratio to receive two injections of 15 mcg A/H5N1 vaccine, 30 mcg A/H5N1 vaccine or placebo. Based on an early comparative analysis of the two cohorts (safety and immunogenicity) through Day 43, the optimal dose level for the Phase 3 will be selected. In Phase 3, the selected dose will be tested in 1,000 subjects, while 500 will receive placebo. Both Phase 2 and B will be double blinded, meaning the study subjects, investigators, and sponsor will be unaware of the treatment allocated to each subject until the clinical trial database is declared final and locked.

4.2 Study Sites

Phase 2 of this study will be conducted at one clinical site in one province and Phase 3 will be conducted in three provinces in Vietnam.

Phase 2

The Phase 2 part of this study will be conducted in the Khanh Hoa Province at Ninh Hoa District Health Center. Data entry/CRF storage will be at the Khanh Hoa Provincial Health Department.

Phase 3

The Phase 3 part of the study will be conducted at three provinces, as follows:

1. Khanh Hoa Province: (same site as Phase 2, but study activities move to the communes)
    - Study activities at the Ninh Da, Ninh Binh, and Ninh Quang Commune health centers.
    - Data entry/CRF storage at the Khanh Hoa Provincial Health Department.
2. Hai Phong Province:
    - Study activities at the Cap Tien, Kien Thiet, and Hung Thang Commune health centers.
    - Data entry/CRF storage at the Hai Phong Preventive Medicine Center.
3. Hoa Binh Province:
    - Study activities at the Hop Kim, Nam Thuong, and Thuong Bi Commune health centers.
    - Data entry/CRF storage at the Hoa Binh Preventive Medicine Center.

For Phase 3, study documents will be stored at the provincial level where data entry will occur, and will be moved to the particular commune health center when a study visit is occurring there.

These locations were satellite sites for several vaccine clinical trials conducted in collaboration with National institute of Hygiene and Epidemiology (NIHE). The staff of the district health center, as well as the staff of the provincial centers in the three provinces have experience in implementing vaccine trials and observational studies on various infectious diseases. They also have experience in working with contract research organizations (CROs), and with local and international sponsors.

According to the health system in Vietnam, three district hospitals of Ninh Hoa, Kim Boi, and Tien Lang, and their corresponding district health centers are under the same management of each Provincial Department of Health of Khanh Hoa, Hoa Binh, and Hai Phong respectively; so it is easy for coordination of care between them should a serious event occur. These district hospitals and commune health centers also have a good capacity in terms of both personnel and equipment that meet requirements for medical care, as well as emergency care, for unexpected adverse events in this trial. The commune health centers conduct routine vaccinations in the community and have the capacity to handle vaccine reactions, in the rare event these would occur. These district health centers and their adjacent hospitals are only about 30-40 kilometers (one hour drive) from provincial general hospitals. This will assure rapid patient transport and referral to tertiary care hospitals at provincial levels in case such referral is necessary. An additional benefit to the study is that specimen transport to the laboratory at Nha Trang Pasteur Institute – a clinical lab for the Phase 2 study (one hour drive from site of Ninh Hoa district) will be convenient, helping to assure specimen quality needed in a rigorous clinical trial.

4.3 Study Product and Other Product to be Used in the Trial (Placebo)

The study product is the inactivated whole virion monovalent A/H5N1 influenza vaccine (IVAC/Nha Trang) or placebo (IVAC/Nha Trang). The vaccine was produced in embryonated eggs, inactivated with formaldehyde, and formulated with 0.6mg aluminum hydroxide in a final volume of 0.5mL single-dose vial. Placebo (PBS, pH 7.2) will also be in 0.5 mL single-dose vial.

4.4 Research Duration

The total time for conduct of the research is approximately 14-16 months. Recruitment and screening is expected to take approximately 5 months (1-1.5 months for the initial cohort and 4-5 months for the remaining cohort). Once enrolled, each subject will be in the study for approximately 3 months (6 weeks of active visits, then passive participation until a phone call at Day 91).

There will be approximately a 8- to 10-month break for an early evaluation of the immunogenicity and safety of the Phase 2 cohort of 300 subjects up to Day 43 before continuing with screening and enrollment of the Phase 3 study cohort.

4.5 Participation Duration

Each participant will be enrolled for approximately 6 weeks of active visits, plus a contact via phone at Day 91 for (a) closure of any ongoing AEs and concomitant medications; and (b) collection of any SAEs and new concomitant medications, if associated with the SAE reported.

4.6 Recruitment and Screening Procedures

4.6.1 Recruitment

Each village keeps population/household register books that contain information on the composition of each family in the village. The commune staff will work with population collaborators/village health workers to make a list of potential study subjects from these register books to identify which households to approach.

Commune staff together with population collaborators/village health workers will go household to household and use information from the information sheet of ICF to highlight the broad concepts of the study and eligibility criteria. They will assess interest of potentially eligible people and create a list from their household visits. These people will be invited to an information meeting to learn more about the study and then investigator/designee will go through the consent sheet again with every single subject and answer the question if any in the private room. Subjects will sign the screening consent, if they are interested.

Individuals who show interest in screening for the study will be invited to the study sites for screening procedures. For Phase 2, each subject must sign ICF-A (screening consent) prior to screening procedures being implemented. For Phase 3, the screening procedures and study procedures are incorporated into one study consent, since there are no laboratory screening tests, and screening and enrollment (vaccination) may occur on the same day. Thus, the study consent must be signed prior to any screening procedures for Phase 3 subjects.

4.6.2 Screening

Study staff will follow inclusion/exclusion criteria to determine eligibility. Screening tests will be offered to all people interested in joining the study (Phase 2 only), and results will be reviewed with them, regardless of eligibility.

Because we cannot predict in advance how many people will agree to screening or agree to join the study, if eligible after screening, it is possible to have more people consented and invited for screening than needed. If this is the case, enrollment will proceed with whomever qualifies and consents first until the study is fully enrolled.

For Phase 2, those who consent to participate in the study will be invited to sign on the ICF-B (study consent). For Phase 3, the study consent will have been signed prior to screening.

4.6.3 Summary of Study Procedures

Screening for Phase 2 Subjects:

1. After obtaining consent for screening, Phase 2 subjects will be screened for eligibility through medical history review, physical examination, testing for serologic evidence of chronic viral hepatitis infection [HBsAg positive or hepatitis C virus (HCV)], and selected biochemical and hematological blood tests. Women who could become pregnant will have a urine pregnancy test performed. There will be 2 screening visits for Phase 2 subjects. The first screening visit (S1) will occur between 5 and 30 days prior to administration of study product at S2/Day 1.
2. Subject screening for eligibility will be completed on the second screening day (S2) for Phase 2 subjects. If a person is found to have a health issue during screening, the staff will advise them on how to get proper treatment. This second screening generally will occur the same day of scheduled enrollment into the trial and administration of study product (Day 1). However, if more time is needed for a study subject to consider participation, Day 1 can be postponed for up to 4 days. Women who could become pregnant will undergo a second urine pregnancy test prior to vaccination on Day 1.

Screening for Phase 3 Subjects:

1. After obtaining consent for the study, subjects will be screened for eligibility through medical history review and physical examination. Women who are able to become pregnant will have a urine pregnancy test performed. If a person is found to have a health issue during screening, the staff will advise them on how to get proper treatment.
2. The screening visit can occur the same day as administration of study product, if the subject agrees, however, Day 1 (vaccination) can be postponed for up to 4 days if more time is needed.

Vaccination and Follow-up Procedures for Phase 2 and Phase 3:

3. **Day 1 Vaccination:** Subjects who are to be vaccinated will undergo targeted physical exam (a physical exam conducted only if symptoms are present) and fertile women will have a urine pregnancy test on the day of vaccination to rule out pregnancy (if Day 1 is separate from screening).

4. Blood specimens will be collected for immunological testing prior to vaccination. In Phase 2, blood specimens will be collected from all study participants (n=300). In Phase 3, blood specimens will be collected from approximately 300 subjects receiving the IVACFLU-A/H5N1 (vaccinees) among 500 enrolled at one of the three provinces, assuming equal enrollment.

5. Study product will be masked so that staff administering it and the subject are unaware of product allocation. The product will be administered and subjects will be carefully monitored for adverse reactions for 30 minutes after vaccination, with a completion of a 30-minute Reactogenicity Assessment.

6. During the first week (Days 1 to 7) following vaccination, subjects will be asked to record local and systemic signs and symptoms using preprinted Diary Cards, a thermometer, and a small ruler. Concomitant medications will also be recorded. In addition to solicited signs, subjects will be asked to report any other adverse events. Members of the investigator's clinical team will visit subjects on Day 2 and call them (or visit, if needed) on Day 6 to check that subjects are correctly completing the Diary Card, to check on the subjects' well-being, and remind the subject to return on Day 8. *Note: For contact with the subject, calling is an acceptable alternative to home visit.*

7. Subjects will return to the study clinic 7 days after injection of study product (on Day 8 +/- 2 days). At that time, the study staff will review the subjects' Diary Cards with them and transcribe all adverse events onto the case report forms. He or she will also do a targeted physical exam that focuses only on reported symptoms from the participant. <u>For Phase 2 subjects only</u>, blood specimens will be collected for clinical safety laboratory tests.

8. Two days before subjects are scheduled to receive Injection 2, subjects will be called to remind them of the next visit to the study clinic and to check on the subjects' well-being.

9. Subjects will return to the study clinic at 3 weeks (with a window of -2/ +4 days) after administration of Injection 1 of study product in order to receive Injection 2. At that time, interim histories and concomitant medications will be reviewed with the participant. Women who are able to become pregnant will again undergo urine pregnancy tests. A targeted physical exam will be performed (based on reported symptoms). For Phase 2 subjects only: (a) blood samples will be collected for clinical safety laboratory tests; and (b) blood serum specimens will be collected for immunologic analyses prior to vaccination. Then subjects will receive Injection 2 of the study product and will be carefully monitored for adverse reactions for 30 minutes after vaccination, with a 30-minute Reactogenicity Assessment performed.

10. After receipt of Injection 2 on Day 22, subjects will again complete Diary Cards for 7 days after vaccination. Members of the investigator's clinical team will phone call (or visit, if needed) on Day 23 and Day 27 to check that subjects are correctly completing Diary Cards and to check on

subjects' well-being. *Note: For contact with the subject, calling is an acceptable alternative to home visit.*

11. Subjects will then return to the study clinic 7 days after Injection 2 (on Day 29 +/- 2 days). At that time, the study staff will review the subjects' Diary Cards with them and transcribe all adverse events onto the case report forms. He or she will also do targeted physical exam that focuses only on reported symptoms from the participant. For Phase 2 subjects only, blood specimens will be collected for clinical safety laboratory tests.
12. Two days before the subjects' next scheduled visit (to occur at 3 weeks after administration of Injection 2), subjects will be called to remind them of the next visit to the study clinic and to check on the subjects' well-being.
13. Subjects will then return to the study clinic at 3 weeks after administration of Injection 2 (Day 43 +/- 4 days) for the last in-clinic visit. At that time, interim histories and concomitant medications will be reviewed with the participant and final blood specimens will be collected for immunogenicity analyses for all subjects included in the immunogenicity subset.
14. On Day 91 (+/- 10 days) subjects will be contacted by phone for (a) closure of any ongoing AEs and concomitant medications; and (b) collection of any SAEs and new concomitant medications, if associated with the SAE reported. This will complete subject participation in the study and subjects will be exited from the study, however, if the subject reports any health problems, the PI may use his or her medical judgment and ask the participant to come to the clinic for an examination or any necessary testing.

4.6.4 Summary of Safety Monitoring

Safety monitoring in this Phase 2/3 study occurs through several mechanisms:

- Continuous review of safety events by the medical staff involved in the study.
- Protocol Safety Review Committee (PSRT) who will monitor the study's safety events on a routine basis (generally weekly).
- Mechanism to pause further injections if certain safety events occur.
- DSMB to determine if, after evaluation of an initial cohort of 300 subject's immunogenicity and safety from Phase 2, it is advisable to continue with the study.

5 Study Enrollment and Withdrawal

5.1 Description of Subjects, Source of Subjects

Approximately 1800 healthy male and female adults, 18 to 60 years of age.

5.2 Subject Inclusion Criteria

The following criteria must be met before a subject may be enrolled for participation:

- Male or female adult 18 through 60 years of age at the enrollment visit.
- Literate (by self-report) and willing to provide written informed consent.
- Healthy adults, as established by the medical history and screening evaluations, including physical examination, capable and willing to complete Diary Cards, and willing to return for all follow-up visits.
- For females able to become pregnant, willing to utilize reliable birth control measures (intrauterine device, hormonal contraception, condoms) through the Day 43 visit.

5.3 Subject Exclusion Criteria

Subjects meeting any of the following criteria will be excluded from participation:

- Participation in another clinical trial involving any vaccine or therapy within the previous three months, or planned enrollment in such a trial during the period of this study.
- Receipt of any non-study vaccine within 4 weeks prior to enrollment or refusal to postpone receipt of such vaccines until after the Day 43 visit.
- Current or recent (within 2 weeks of enrollment) acute illness with or without fever.
- Receipt of immune globulin or other blood products within 3 months prior to study enrollment or planned receipt of such products prior to the Day 43 visit.
- Chronic administration (defined as more than 14 consecutively-prescribed days) of immunosuppressants or other immune-modulating therapy within six months prior to study enrollment. (For corticosteroids, this means prednisone or equivalent, ≥ 0.5 mg per kg per day; topical or intranasal steroids are allowed.)
- History of asthma.
- Hypersensitivity after previous administration of any vaccine.
- Suspected or known hypersensitivity to any of the study vaccine components, including chicken or egg protein, antibiotics, and rubber (from the vaccine vial stoppers).
- Acute or chronic clinically significant pulmonary, cardiovascular, hepatobiliary, metabolic, neurologic, psychiatric, or renal functional abnormality, as determined by medical history, physical examination, or clinical laboratory screening tests, which in the opinion of the investigator, might interfere with the study objectives.
- History of any blood or solid organ cancer.
- History of thrombocytopenic purpura or known bleeding disorder.
- History of seizures.
- Known or suspected immunosuppressed or immune deficient condition of any kind.

- Known HBV or HCV infection by self-report (Phase 3) or a positive test for either Hepatitis B virus surface antigen (HBsAg) or HCV antibody using anti-HCV test (Phase 2).
- Known HIV infection (self-report)
- Known active tuberculosis or symptoms of active tuberculosis (self-report).
- History of chronic alcohol abuse and/or illegal drug use.
- Pregnancy or lactation (a negative pregnancy test will be required before administration of study product for all women of childbearing potential).
- History of Guillain-Barre Syndrome.
- Any condition in the opinion of the investigator that would increase the health risk of the subject if he/she participates in the study or interfere with the evaluation of the study objectives.

Note: Minor out-of-range laboratory values no greater than Grade 1 (see toxicity table in Appendix) will not be considered to be exclusionary at screening.

5.4 Treatment Assignment Procedures

5.4.1 Randomized Procedure

This is a double-blind, randomized, and controlled trial with a 1:1:1 ratio among three groups in Phase 2: 15 mcg/mL vaccine, 30 mcg/mL vaccine, and placebo; and 2:1 ratio between two groups in Phase 3: either 15 mcg/mL or 30 mcg/mL vaccine and placebo. Each subject will be assigned a unique screening number by the investigator after signing the informed consent.

The Investigator will maintain the screening/enrollment log. The log will contain essential information including subject name, date of screening, gender, date of birth, whether or not the subject meets eligibility criteria, whether subject is enrolled and date, and if not enrolled, reason why the subject is not enrolled or not randomized.

Once a subject identification number has been assigned to a subject, it will not be used again. Additional subjects may be randomized into the study at the discretion of the sponsor in the case of any subject who is randomized but does not receive any study vaccine.

The permuted randomization block design procedure will be used to generate the randomization schedules for both Phase 2 and Phase 3. The randomization will be stratified by province and age group (18-40 years of age and 41-60 years age). The block size for each part will be chosen based on the number of treatment groups and anticipated enrollment sizes at each province.

5.4.2 Blinding and Unblinding Procedures

The mechanics of randomization will be conducted by an entity that is not involved with trial follow-up or monitoring. Details of the mechanics of randomization will not be provided in the protocol or to any staff implementing the trial in order to assure integrity of the data.

The randomization lists for subjects will be used by IVAC to label study vaccine and placebo vials, and then will be immediately sealed. It will be opened only after the clinical trial database is declared

complete and locked. In the case of any unblinding, researchers must report this in writing to the sponsor and overseeing Ethics Committee.

IVAC vaccine and placebo vials will be packaged and labeled in such a way that they have similar appearance. However, IVACFLU-A/H5N1 vaccine uses aluminum hydroxide as an adjuvant and the placebo is phosphate buffered saline (PBS), so there will be a slight difference in the appearance between vaccine and placebo. To address the blinding issue, in addition to the original vial label of the vaccine and placebo designed by IVAC in compliance with the drug labeling regulations of the Ministry of Health, an identical study label designed for experimental vaccine and placebo containing only the study product code of each subject will be pasted over the original vial label to ensure implementation of double blinding. The labeling will be done at IVAC before study vaccine and placebo are shipped to the study site. To blind the vaccinator and study subjects, a nurse will be recruited and trained to be responsible for withdrawing study product from vials according the randomization schedule in a separate room/closed private space, then masking the syringe before handing over to vaccinator. A SOP on this procedure will be developed to ensure the double-blind of this study. This nurse will not participate in any safety evaluation of study subjects.

Study product injected into each subject will be recorded using the exact allocation code for each product received by each subject.

The allocation codes which link treatment identification with each subject via subject identification numbers will be maintained in a secure location and managed by individuals who are not directly implementing or monitoring the trial. The allocation code listing will not be opened or linked to the clinical trial database until after all databases are locked. All blinded study staff will remain blinded throughout the trial. If any subject experiences an SAE possibly related to receipt of study treatment, treatment allocation to the subject may be communicated to the investigator only if that information is deemed necessary to properly treat the subject for the SAE. Written procedures for blinding, storage, and opening of study codes, in compliance with the approved protocol, will be developed to ensure the study is not unnecessarily unblinded.

5.4.3 Early Termination

An enrolled/vaccinated subject may be terminated from the study for any of these reasons:

a) Subject withdraws consent.

b) PI or a medical monitor involved in the study decides that termination is in the best interest of the subject.

c) PI or a medical monitor involved in the study decides that termination is necessary to protect the integrity of the study or achieve the objectives of the study.

d) Interruption of study schedule makes the subject’s data unusable according to protocol requirements.

e) Sponsor terminates the study.

f) Governing IRBs recommends to terminate the study

If a subject withdraws from the study for any reason prior to the planned study duration, every attempt is made to complete the following:

a) Report of local and systemic reactogenicity and AEs are reviewed by PI (or designee).
b) Obtain specimens for immunogenicity analysis if withdrawal occurs prior to scheduled laboratory testing.
c) Diary Card information is reviewed with the subject in detail by site staff, if in use since the last visit.
d) Injection site(s) examination and a targeted physical examination are performed (if indicated).

IVAC must be informed within 48 hours of all instances of the premature termination of a subject's participation in the trial.

If the subject develops a reaction to study vaccine which the investigator believes threatens the subject's well-being, the withdrawn subject must be treated or transferred to a treatment facility.

Study Termination: IVAC retains the right to temporarily suspend or prematurely discontinue this study at any time related to safety. If the study is stopped or suspended prematurely, IVAC will inform the local Principal Investigator as well as regulatory authorities about the decision and the reasons for termination or suspension. If such action is taken, all efforts must be made to ensure the safety of the subjects enrolled in the study. The Principal Investigator will assist IVAC in informing the responsible IEC and provide the reason for the suspension or termination. In case of premature study or study site closure, the monitor will conduct all activities for final monitoring visits.

6 Study Products

6.1 Study Product Descriptions

6.1.1 Study Vaccine

IVACFLU-A/H5N1 is an influenza A/H5N1 vaccine produced by IVAC using embryonated chicken eggs. IVACFLU-A/H5N1 is a whole virus vaccine, collected in a linear sucrose density gradient solution using a continuous flow centrifuge (Alfa Wassermann, West Caldwell, NJ) and inactivated with formaldehyde. Vaccine strain NIBRG-14 derived from original influenza A/ Vietnam/1194/2004 was provided to IVAC by the National Institute for Biological Standards and Control of the Health Protection Agency of the United Kingdom.

6.1.2 Formulation, Packaging and Labeling (Product Name and Trademark)

IVACFLU-A/H5N1 is formulated to contain either 15 mcg hemagglutinin (HA) and 0.6 mg of aluminum hydroxide adjuvant per 0.5 mL dose, or 30 mcg hemagglutinin (HA) and 0.6 mg of aluminum hydroxide adjuvant per 0.5 mL dose. It is filled in single dose vials. Each 0.5 mL dose may contain residual amounts of formaldehyde (not more than 0.02%) and sucrose (not more than 0.2%).

IVACFLU-H5N1 has a sterile, slightly opalescent suspension after shaking well. Antibiotics are not used in the manufacture of IVACFLU-A/H5N1. IVACFLU-A/H5N1 does not contain latex. The future package insert will describe the vaccine as follows:

Product name:	A/H5N1 Influenza vaccine
Trademark:	IVACFLU-A/H5N1
Active substance:	Virus particles containing hemagglutinin (HA)
Formulation:	15 mcg HA in 0.5 mL PBS pH 7.2 or 30 mcg HA in 0.5 ml PBS pH 7.2 Aluminum hydroxide 0.6 mg in 0.5 mL
Product form:	Purified whole virus, inactivated, with adjuvant (Aluminum Hydroxide).
Pharmaceutical form:	Injectable biologic
Administration route:	Intramuscular (IM)
Dosage:	0.5 mL, 2 injections, 21 days apart
Packaging:	10 single-dose vials per box*
Storage:	From + 2^{O}C to+ 8^{O}C, avoid freezing

**Because of the need for blinding of vaccine and placebo, packaging in this trial may be different.*

6.1.3 Placebo

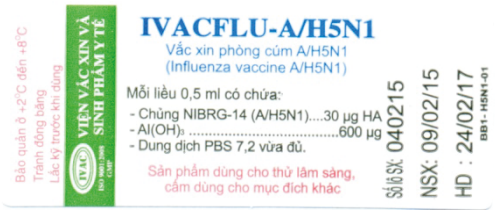
Placebo (PBS) will be manufactured by IVAC. PBS, pH 7.2, will also be in 0.5 mL single-dose vials.

NaCl	4.500 mg
$Na_2HPO_4.2H_2O$	0.685 mg
$NaH_2PO_4.2H_2O$	0.186 mg
Water For Injection (qs)	0.5 mL

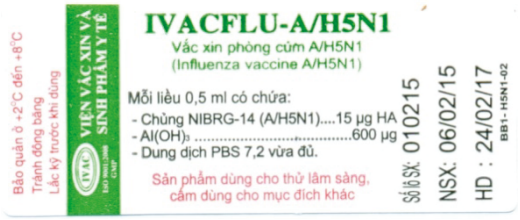
6.1.4 Packaging

IVACFLU-A/H5N1 vaccine and placebo will be filled in glass vials at a dose volume of 0.5 ml, and covered with a pharmaceutically acceptable rubber stopper, an aluminum cap seal, and single-use flip-off plastic lid. Packaging will be done to assure that the vials are intact and vaccine of high quality. A continuous temperature data logger will be placed inside each carton box to monitor product temperature during the process of transportation, storage, and delivery of the product. The carton boxes will also have "product to be used for clinical trial purposes only" label and information on the product storage temperature (from +2°C to +8°C). The sample label is below:

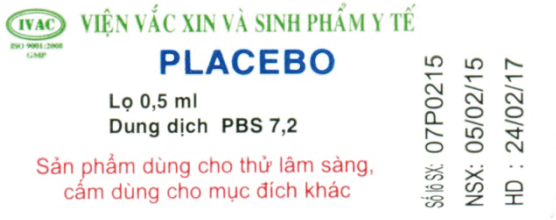
- Label of IVACFLU-A/H5N1 vaccine containing the 30 µg HA/dose (0.5 ml)



- Label of IVACFLU-A/H5N1 vaccine containing the 15 µg HA/dose (0.5 ml)



- Label of the Placebo



The study product must not be used if the package or labeling appears to be tampered with, the label is illegible, or the physical properties (color and transparency) are altered. These labels will be overlabeled with a blinded randomization code, similar to what is shown below.

6.1.5 Stability and Storage

Study product must be stored at a temperature between +2 degrees Celsius (°C) to +8°C. The shelf-life is 24 months in that condition. Storage temperature must be monitored daily and documented on an appropriate form. Back-up power or storage must be available in case of primary power failure. Study

vaccine and placebo must never be frozen. Their temperature will be monitored at the manufacturer, during transport, and at the clinical trial site.

In case of accidental disruption of the cold chain, the products may not be administered and the investigator or the responsible person should contact IVAC to receive further instructions. In such cases, the investigator must receive written consent (through facsimile or emailed, scanned copy) of IVAC before any study product may be used.

6.1.6 Lot Number, Expiry Date, and Quality Control Results of Study Vaccine Lots

The vaccine study lots and placebo study lots have passed quality control testing performed by the National Institute of Control Vaccine and Medical Biologicals, Vietnam. See Appendix C for the results.

6.2 Dosage, Preparation, and Administration of Study Products

6.2.1 Dosage and Schedule

Each dose will total 0.5 mL containing either 15 mcg or 30 mcg of HA, and delivered intramuscularly into the deltoid of the non-dominant arm. In this study, in order to monitor local reactions, each dose will be injected into the deltoid of the non-dominant arm, unless the deltoid of the non-dominant arm area is not ideal for injection/reactogenicity or the subject prefers the injection in the other arm.

Each dose will be administered 21 days apart in this study.

6.2.2 Precautions and Warnings

1. IVACFLU-A/H5N1 is only to be used for healthy adults 18 to 60 years of age participating in this study. It is forbidden to use the vaccine for any other purpose.
2. Strict compliance with the regulations of the MOH on the use of vaccines and biologicals is required (Decision No.12/2014/TT-BYT, dated 20/03/2014).
3. Vaccination of each 0.5 mL dose must be intramuscularly into the deltoid of the non-dominant arm, not intravenously or subcutaneously.
4. Study product vials that have been frozen may not be used.
5. IVACFLU-A/H5N1 or placebo solution is a homogenous preparation, transparent or clear white in appearance. Do not inject if the study product vial appears to have unusual content or if the liquid in the vials has changed color.
6. Only health workers who have been trained in the framework of this research may administer study product to subjects participating in the research, assuring proper intramuscular injection technique and sterile injection.
7. Only one person may be injected with one needle and syringe.

8. During vaccination, researchers must supervise vaccination activities and record observations of post-vaccination monitoring of subjects.
9. Study subjects must be monitored during vaccination and 30 minutes afterwards.
10. During study vaccinations, there must be adequate facilities for monitoring and treating any reactions. Drugs to treat anaphylaxis must be available, as must specialist doctors for such an emergency.

6.2.3 Preparation and Administration

To prepare and administer study product, vaccination facilities and investigators must comply with Ministry of Health regulations (No.12/2014/TT-BYT, dated 20/03/2014). The step-by-step instructions for the investigator are as follows:

1. Wash hands. Prepare the study vaccine/placebo, needles, syringes, and sharps safety box ahead of time.
2. In order to preserve the study blind, a qualified, specially trained staff member (nurse or physician) will prepare the study product for administration immediately before administration. This will be a different person than the one who evaluates reactogenicity of the subject. Specific study procedures will be developed, including selecting the appropriate vial for each subject, gently shaking the vaccine vial, withdrawing the 0.5-mL dose of study vaccine/placebo from the vial using a sterile needle and syringe, labeling the syringe with subject identification number, and occluding the contents of the syringe. Careful records must be maintained to ensure and document that each subject receives the correct dose. Once the dose vial has been penetrated, the withdrawn study vaccine/placebo should be used promptly.
3. Make sure you have sufficient equipment to provide every subject with a safe injection and to dispose of injection materials safely.
4. Make sure you have emergency drug and equipment kits in both the vaccination area and the observation area.
5. Greet the subject in a friendly manner. Ask whether he/she has any questions or concerns about immunization and respond to his/her questions or concerns in a truthful, pleasant manner.
6. Confirm the subject identity.
7. Ensure the subject is seated.
8. Ask the subject about his/her handedness and record this information on the CRF.
9. Inform the subject that for consistency in the study, all subjects will be vaccinated in the deltoid of the non-dominant arm.
10. Instruct the subject to put the non-dominant arm on the hip and show the deltoid of the non-dominant arm.
11. Disinfect the skin at the injection site.

12. Inject intramuscularly the entire contents of the syringe into the deltoid region of the upper non-dominant arm.
13. While the plunger is still depressed, remove the needle from the subject's arm.
14. Apply cotton swab with pressure to the injection site. Do not put sticking plaster onto the injection site.
15. Do not recap the needle. Dispose of the needle and syringe in a sharps container. Store the empty vial in a safe place (not the refrigerator) until the end of the study. The vial must not be disposed of until monitors have verified that it is allowed.
16. Record the date of vaccination and vaccine vial number on the subject's vaccination card.
17. Ask the subject to rest for 30 minutes.
18. While the subject is resting, explain how to use the Diary Card for recording any symptoms.
19. After 30 minutes, observe the subject and ask about the subject's well-being.

6.3 Modification of Study Product for a Subject

There is no dose adjustment for the product in the study.

6.4 Accountability Procedures for Study Product

The study vaccine and placebo will be kept in a secure place, in cold storage, and segregated from other products at the study clinic. During the study, the investigator or the person in charge of research product management will record information related to the delivery of vaccine and placebo to the trial site, conduct inventory at the trial site, check the number of doses given to the participants, check the number of unused doses, and return the unused doses to IVAC upon completion of the study.

At the Vaccination Site

- On scheduled vaccination days, study vaccine and placebo will be transported to the local site with proper temperature control and monitoring.
- Standard procedures will be followed at the trial site to maintain proper transport, receipt, storage, and return of study products.
- In the case of interruption of the cold chain (i.e., the temperature is out of acceptable range), the Principal Investigator or qualified designated staff member must contact IVAC to get further instructions. The investigator must receive written consent (through facsimile or emailed scanned copy) from IVAC before clinical trial products can be used.

6.5 Assessment of Compliance with Use of the Study Products

Compliance with use of the study products will be closely monitored during the trial by the research team, IVAC, and trial monitors.

6.6 Concomitant Medications/Treatment

Concomitant medications will be documented through Day 43 of the study and then at Day 91 only for medications taken for SAEs.

Treatment of conditions that are not exclusionary should continue, if needed by the subject. Subsequent changes in concomitant treatment during the trial must also be reflected in the CRF.

Women included in the trial who are using hormonal contraception for pregnancy prevention should continue taking these products during the entire trial. Use of such products must also be documented in the CRF.

6.7 Unauthorized Products

The following products are not authorized to be used during the study:

1. Any concomitant medicine or biologic specifically prescribed for the treatment of a condition which is an exclusion criterion for participation in the trial.
2. All non-study vaccines or biologics (including blood products).

Other concomitant medications will be reviewed on a case-by-case basis if the study staff are unclear.

Subjects will be requested not to take analgesic or antipyretic drugs *in a preventive way* (before or soon after injection), as such medications might change the reactogenicity profiles of study vaccine and placebo.

During the trial, if a situation arises where there is an adverse reaction or AE requiring treatment and prescription of unauthorized products or products not stipulated by the protocol, then such products may be prescribed. However, IVAC must be informed of such an occurrence within 48 hours. Information on the products (trade name, dosing or change in dosing, indications, start date, and termination date) must be recorded in the CRF.

7 Study Schedule; Description of Visits

The total expected duration of the study:

First subject enrolled in study	Day 1 of first subject
The last subject enrolled in study	For Phase 2: Day 1 of last subject is estimated 2-4 weeks from Day 1 of first subject; Phase 3: Day 1 of last subject is estimated approximately 18 months after the Day 1 of first subject from Phase 2.
The last subject completes the trial	Day 91 of last subject
Lock database	8 weeks after Day 91 of last subject for each Phase
Clinical trial report	8-10 months after Day 91 of last subject for Phase 3

7.1 Screening: Phase 2 Subjects

Prior to inclusion into the vaccine study, each subject will be screened by laboratory testing, medical history interview, and physical examination. Because screening procedures are required to assess eligibility, they will be performed under a screening informed consent form (ICF A) for Phase 2 subjects prior to the subject providing informed consent for study participation (ICF B). The investigator will record the screening IDs of all participants who enter screening; whether they entered the trial or failed screening, and the reason for screen failure on the screening/enrollment log.

7.1.1 First Screening Visit (Day S1)—Phase 2

The first screening visits can occur from 30 days to 3 days before S2/D1.

After subjects are consented into the screening process (using ICF A), the following activities will occur:

1. The subject will be interviewed to collect baseline demographic data.
2. A study clinician will interview the subject to collect a detailed medical history, focusing on current medical conditions. Study staff will review the information to confirm eligibility prior to conduct of further procedures.
3. A study clinician will perform a general physical examination. Results will be reviewed by study staff and with the subject to confirm eligibility prior to conduct of further procedures. If a person is considered ineligible based on medical history and physical examination, the study clinician will tell the person that he or she is not eligible; however, if they would like, the study can conduct the laboratory screening tests and provide results to them or their regular physician.
4. Blood (serum and whole) specimens will be collected for biochemical and hematological testing. Serum specimens will also be collected for testing for chronic viral hepatitis infections. Specimen collection information must be documented in appropriate source documents/CRFs.
5. For women able to become pregnant, a urine pregnancy test will be done.
6. Study staff will instruct the subject on when to return for screening results and for possible enrollment into the vaccination phase of the study.

7.1.2 Second Screening Visit (Day S2; Day 1 or Day 1 -4)—Phase 2

Subjects will have a second screening (S2) visit to verify their eligibility. Generally, the second screening visit and the first injection will occur on the same day. However, a 4-day window is allowed in case more time is needed. For each subject continuing with the screening process, the following activities will occur on Day S2:

1. The subject comes to the study clinic at the specified time. Study staff will confirm subject identity.

2. Laboratory and hepatitis serology results will be reviewed by a study clinician and with the subject. All results will be reviewed to confirm eligibility prior to conduct of further procedures. If a person is found to have a health issue during screening, the staff will advise them on how to get proper treatment.
3. For women able to become pregnant, a urine specimen will be collected for pregnancy testing.
4. Study staff will inquire about any new medical events since medical histories were recorded and confirm eligibility prior to conduct of further procedures.
5. A study clinician will perform a targeted physical examination (performed only if symptoms are present). Results will be reviewed by study staff and with the subject to confirm eligibility prior to conduct of further procedures.
6. If eligibility is confirmed, all information since the beginning of screening must be recorded on the study CRFs.

7.2 Screening: Phase 3 Subjects (S1/Day 1 or Day 1 -4)

Phase 3 subjects will sign one study consent before screening that covers both screening and study procedures. The investigator will record the screening IDs of all participants who enter screening; whether they entered the trial or failed screening, and the reason for screen failure on the screening/enrollment log. If a person is found to have a health issue during screening, the staff will advise them on how to get proper treatment.

For Phase 3 subjects, there is only one screening visit and it can occur on the same day as vaccination (Day 1), if the subject agrees. If not, the window for the screening visit allows Day 1 to occur up to 4 days after the screening visit.

After subjects are consented, the following activities will occur:

1. The subject will be interviewed to collect baseline demographic data.
2. A study clinician will interview the subject to collect a detailed medical history, focusing on current medical conditions. Study staff will review the information to confirm eligibility prior to conduct of further procedures.
3. A study clinician will perform a general physical examination. Results will be reviewed by study staff and with the subject to confirm eligibility prior to conduct of further procedures.
4. For women able to become pregnant, a urine pregnancy test will be done.
5. If eligibility is confirmed, all information since the beginning of screening must be recorded on the study CRFs.

7.3 Vaccination and Follow-up Periods: Phase 2 and Phase 3

7.3.1 First Vaccination (Day 1; S2 or S2 + 4 (Phase 2) or S1 or S1 + 4 (Phase 3))

Day 1 is the day of injection of the study product. For Phase 2 subjects, it can occur on Day S2 or up to 4

days after S2, if more time is needed for a potential subject to decide whether to join the study or if screening needs to be repeated. For Phase 3 subjects, it can occur the same day as screening or up to 4 days after, if the subject requires more time to consider vaccination. Note: The sites for blood draw and injection may be reversed if it is needed for proper injection and assessment of reactogenicity, or if the subject has a strong preference for the injection to be in the dominant arm.

1. If Day 1 is separate from S2 (or the screening visit for Phase 3), the study clinician must reconfirm subject identity and eligibility of the subject, including a urine pregnancy test for women who could become pregnant.
2. A study clinician will review the procedures for the vaccination study with each eligible subject. For Phase 2 subjects, a vaccine study ICF (ICF B) must be completed at this time (Phase 3 subjects have already signed the study consent). Upon entry into the trial portion of the study, the subject is assigned an ID number and may proceed to undergo further procedures related to administration of study product and evaluation of vaccine safety and immunogenicity.
3. A study clinician will perform a targeted physical examination (performed only if symptoms are present).
4. Prior to administration of study product, a serum specimen will be collected from the subject's dominant arm for anti-influenza serologic assays. This includes all subjects for Phase 2 and 1 of 3 clinical sites in Phase 3.
5. The subject will be administered one injection of study product in the deltoid of the non-dominant arm. (Injection may be given in the dominant arm if subject prefers.)
6. The subject will be observed for 30 minutes after administration in case of any immediate reactions. If the subject experiences an immediate adverse reaction, he/she will be treated and the event will be recorded on the CRF. A 30-minute Reactogenicity Assessment will be completed.
7. The subject will be given a Diary Card (and thermometer and ruler) in which the subject will be asked to record any local and/or systemic reactions that might appear from Days 1 to Day 7, and record any concomitant medications. The subject will be instructed how to use the Diary Card, thermometer and ruler. All relevant explanations should be included in the Diary Card. The Diary Card will also have contact information for the investigators, should the subject have any questions. The subject will be informed that a member of the investigator's team will visit or call the subject the next day (Day 2) and then call (or visit, if needed) 5 days after the injection (Day 6) to check on the subject's completion of the Diary Card and subject's well-being.
8. The subject will be instructed that if the subject later experiences an AE requiring medical care, the subject should inform the investigator as soon as possible and seek medical care as appropriate. If the subject visits a health care provider, the subject should be sure to inform the health care provider of participation in this study and provide the health care provider with the investigator's contact information.

7.3.2 First Week After Injection 1 (Day 1-7)

1. The subject will complete the Diary Card daily, reporting any local or systemic reactions experienced and medications taken from the evening of D1 through D7 after vaccination.
2. The subject will have been instructed that if he/she experiences an AE requiring medical care, the subject should inform the investigator as soon as possible and seek medical care as appropriate. If the subject visits a health care provider, the subject should be sure to inform the health care provider of participation in this study and provide the health care provider with the investigator's contact information.
3. At Day 2 post vaccination, a member of the investigator's clinical team will visit or call the subject to check that the subject is correctly completing the Diary Card and to check on the subject's well-being. At Day 6, the subject will be called (or visited, if needed) to again check on completion of the Diary Card and check on his or her status. *Note: For contact with the subject, calling is an acceptable alternative to home visit.*

7.3.3 Seventh Day after Injection 1 (Day 8 ± 2)

1. Study staff will confirm subject identity.
2. Study staff will review the subject Diary Card and interim history with the subject and inquire about any new medical events since medical histories were last updated. Any AEs that have occurred will be recorded in the appropriate section(s) of the CRF. Study staff will collect the Diary Card and keep it as a source document.
3. A study clinician will perform a targeted physical examination and record the information on the CRF. Results will be reviewed by study staff and discussed with the subject. Any AEs that have occurred will be recorded in the appropriate section(s) of the CRF.
4. **FOR PHASE 2 SUBJECTS ONLY:** If not done previously, the study clinician will review the results of the selected biochemical and hematological tests conducted from the blood drawn on S1 with the subject.
5. **FOR PHASE 2 SUBJECTS ONLY: Blood is collected for clinical safety laboratory testing** (ALT, creatinine, bilirubin, hemoglobin, and white cell and platelet counts)**.** Specimen collection information must be documented on the CRF and in specimen collection forms.
6. The subject will be instructed that if the subject later experiences an AE requiring medical care, the subject should inform the investigator as soon as possible and seek medical care as appropriate. If the subject visits a health care provider, the subject should be sure to inform the health care provider of participation in this study and give the health care provider the contact information for the investigator.

7.3.4 Second and Third Weeks After Injection 1 (Day 8-21)

The subject will have been instructed that if he/she experiences an AE requiring medical care, the subject should inform the investigator as soon as possible and seek medical care as appropriate. If the subject visits a health care provider, the subject should be sure to inform the health care provider of participation in this study and give the health care provider the contact information for the investigator.

7.3.5 Second Vaccination (Day 22; ±2 days)

1. Study staff will confirm subject identity.
2. Study staff will review interim medical histories and concomitant medications with the subject since medical histories were last updated.
3. **PHASE 2 SUBJECTS ONLY:** (a) Blood specimens will be collected for clinical safety tests; and (b) blood specimens will be collected for anti-influenza serologic assays. Blood specimens will be collected from the dominant arm. Specimen collection information must be documented on the appropriate source documents/study forms. .
4. For women who could become pregnant, a urine specimen will be collected for pregnancy testing. A positive result is recorded on a Pregnancy Report Form and vaccination withheld.
5. A study clinician will perform a targeted physical examination (an exam based on subject symptoms) and record the information on the CRF. Results will be reviewed by study staff and discussed with the subject. Any AEs that have occurred will be recorded in the appropriate section(s) of the CRF.
6. The subject will be administered one injection of study product in the deltoid of the non-dominant arm.
7. The subject will be observed for 30 minutes after administration in case of any immediate reactions. If the subject experiences an immediate adverse reaction, he/she will be treated and the event will be recorded on the CRF. A 30-minute Reactogenicity Assessment will be completed.
8. The subject will be given a Diary Card in which the subject will be asked to record any local and/or systemic reactions that might appear from Day 22 to Day 28 and to record any concomitant medications. Subjects will be instructed how to use the Diary Card. All relevant explanations should be included in the Diary Card. The Diary Card will also have contact information for the investigators, should the subject have any questions. The subject will be informed that a member of the investigator's team will visit or call the subject one and five days later to check on the subject's completion of the Diary Card and subject's well-being.
9. The subject will be instructed that if he or she later experiences an AE requiring medical care, they should inform the investigator as soon as possible and seek medical care as appropriate. If the subject visits a health care provider, the subject should be sure to inform the health care provider of participation in this study and give the health care provider the contact information for the investigator.

7.3.6 First Week After Injection 2 (Days 22-28)

1. The subject will complete Diary Card of any local or systemic reactions experienced; from the evening of D22 through D29 after vaccination.
2. The subject will have been instructed that if he/she experiences an AE requiring medical care, the subject should inform the investigator as soon as possible and seek medical care as appropriate. If the subject visits a health care provider, the subject should be sure to inform the health care provider of participation in this study and give the health care provider the contact information for the investigator.
3. At Day 23, a member of the investigator's clinical team will call the subject (or visit, if needed) to check that the subject is correctly completing the Diary Card and to check on the subject's well-being. At Day 27, the subject will be called (or visited, if needed) to again check on completion of the Diary Card, check on his or her status, and reminded of the study visit for the next day. *Note: For contact with the subject, calling is an acceptable alternative to home visit.*

7.3.7 Seventh Day After Injection 2 (Day 29±2 days)

1. Study staff will confirm subject identity.
2. Study staff will review the Diary Card and interim history with the subject and inquire about any new medical events since medical histories were last updated. Any AEs that have occurred will be recorded in the appropriate section(s) of the CRF. Study staff will collect the Diary Card and keep it as a source document.
3. A study clinician will perform a targeted physical examination (based on any reported symptoms) and record the information on the CRF. Results will be reviewed by study staff and discussed with the subject. Any AEs that have occurred will be recorded in the appropriate section(s) of the CRF.
4. **FOR PHASE 2 SUBJECTS ONLY:** (a) If not done previously, a study clinician will review the results of the Day 22 clinical safety lab tests with the subject; and (b) blood is collected again for selected clinical safety tests (ALT, creatinine, bilirubin, hemoglobin, and white cell and platelet counts)**.** Specimen collection information must be documented on appropriate source documents/study forms.
5. The subject will be instructed that if the subject later experiences an AE requiring medical care, the subject should inform the investigator as soon as possible and seek medical care as appropriate. If the subject visits a health care provider, the subject should be sure to inform the health care provider of participation in this study and give the health care provider the contact information for the investigator.

7.3.8 Second and Third Weeks After Injection 2 (Days 29-42)

There are no formal study visits during this time. The subject will have been instructed that if he/she experiences an AE requiring medical care, the subject should inform the investigator as soon as possible

and seek medical care as appropriate. If the subject visits a health care provider, the subject should be sure to inform the health care provider of participation in this study and give the health care provider the contact information for the investigator.

7.3.9 Final Immunogenicity Visit (Day 43 ±4 days)

1. Study staff will confirm subject identity.
2. Study staff will review interim medical histories and concomitant medications with the subject since medical histories were last updated. *This is the last time any new AE information will be entered into the database, except for collection and reporting of SAEs and updates on existing AEs.*
3. **FOR PHASE 2 SUBJECTS and SUBJECTS FROM ONE PHASE 3 SITE:** Blood specimens will be collected for anti-influenza serologic assays. Specimen collection information must be documented on appropriate source documents/study forms. **FOR PHASE 2 SUBJECTS ONLY:** If not done previously, the study clinician will review the results of the clinical safety laboratory tests conducted from the blood drawn on D29 with the subject.
4. A study clinician will perform a targeted physical examination (based only on reported symptoms) and record the information on the CRF. Results will be reviewed with the subject and any AEs that have occurred will be recorded in the appropriate section(s) of the CRF.
5. The subject will be told that he or she will be called by a member of the study team at Day 91 to ask how he or she is doing and if they have had any specific health issues.

7.3.10 Final Study Visit (Day 91; ± 10)

1. The subject will be contacted via telephone and identity confirmed.
2. Study staff will review interim medical histories and concomitant medications with the subject since these were last updated. The staff will seek the status of any AEs that were considered ongoing at the Day 43 visit. No new concomitant medication will be recorded unless it relates to a newly identified SAE.
3. Study staff will ask about any medical event that would constitute an SAE since the last visit. No new AE information will be recorded unless it qualifies as an SAE.
4. If an SAE is reported, the clinician should record the SAE on the appropriate form, notify the entities who require notification, and refer the participant for treatment of the SAE, if warranted.
5. After recording the information, the subject will be discharged from the study.

7.4 Unscheduled Visits

Subjects may present to the study center during operating hours for an unscheduled visit should they experience any AE, or if the subject's condition requires medical intervention or a retesting of specimens

for Phase 2 subjects. Data for any examinations performed on the subject at an unscheduled visit must be recorded in the CRF.

8 Study Evaluations

8.1 Clinical Evaluations

8.1.1 Definition and Categorization of AEs

The primary objective of this study is to describe the safety profile of two intramuscular doses of IVACFLU-A/H5N1. An AE is defined as any untoward medical occurrence in a patient or clinical investigation participant administered a pharmaceutical product, which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. Grading of AEs is also described in this section. Included below are brief listings of specific clinical and laboratory safety measurements to be made. All clinical safety evaluations must be made by a qualified clinician (physician, physician assistant, or nurse practitioner) or will be self-reported by the subject. Serious adverse events may occur at any time during the study. They are defined in Section 9.2.8.

8.1.2 Specific Clinical Signs and Symptoms of Interest

All clinical signs and symptoms must be documented. Specific signs and symptoms of interest, and their time and date of onset/occurrence and resolution, will be solicited and recorded for all subjects from the time of signing ICF B until termination of participation. These are listed in Section 9.2.6 as Solicited Local and Systemic Reactions.

These evaluations will be made by a clinician on Days 1, 8, 22, 29, and 43. Evaluation must be performed both prior to and after administration of study product on Days 1 and 22. Reported signs and symptoms will be recorded by the subject on Diary Card from Days 1-7 and Days 22-28 in the study.

8.1.3 Medical History

At enrollment, medical histories must be thoroughly reviewed with the subject. The following medical conditions, in particular, will be assessed:

- Current or recent (within two weeks of enrollment) acute respiratory illness with or without fever.
- Recent vaccination history.
- Recent receipt of immune globulin or other blood products, or injected or oral corticosteroids, or other immune modulator therapy within 6 weeks (before) of enrollment.
- Hypersensitivity of any kind.
- Asthma.

- Clinically relevant history of renal, gastrointestinal, hepatic, cardiovascular, hematological, dermatological, endocrine, neurological, or immunological diseases.
- Seizures, including history of febrile seizures, or any other neurologic disorder.
- Known or suspected immunologic impairment of any kind.
- Known HIV infection.
- Known HBV or HCV infection.
- Alcohol or drug use.
- Medications taken in the 2 months (including trade name, dosing or change in dosing, indications, start date, and termination date).
- For women, pregnancy, menstrual, and contraceptive history and/or history of surgical sterility.

8.1.4 Physical Examination

General Physical Examinations

A General Physical Exam is performed on Day S1 and anytime it is clinically indicated according to the medical judgment of the study staff. Qualified study clinicians will conduct a physical examination of all subjects. This physical examination will include the following:

- Recording of general appearance.
- Physical examination of all organ systems. This includes the following:
  - Neurologic examination, including cranial nerve examination
  - Chest auscultation
  - Examination of lymph nodes (axillary and cervical)
  - Heart auscultation
  - Abdomen palpation (to check for liver size)
- Measurement of the following vital signs:
  - Body temperature (and body location of measurement)
  - Blood pressure
  - Pulse/heart rate

Targeted Physical Examinations

Targeted physical examinations (focused on symptoms reported by the subject) will be made by a clinician on Day 1, 8, 22, 29, and 43 and, if possible, any time a subject leaves the study early. Evaluation must be made prior to administration of injection of study product on Day 1 and 22. Targeted exams will include these measurements, plus evaluation of any physical complaints of the subjects.

- Measurement of the following vital signs:
  - Body temperature (and body location of measurement)
  - Blood pressure
  - Pulse/heart rate

8.2 Laboratory Evaluations

8.2.1 Clinical Laboratory Evaluations

All biochemical, immunological, and hematological testing will be performed at labs that have been certified within Vietnam. Some samples may be sent to an additional lab for feedback and assistance to the Vietnam laboratory on testing methods. These outside test results are for technical assistance only and will not be considered in the analysis.

Laboratories will follow written procedures for conducting all laboratory assays.

Laboratory reference ranges will be specified for all tests prior to enrollment of any subject. The reference ranges will be developed based on a survey of ranges from national and regional hospital laboratories. A Toxicity Grading Table will be used to facilitate the grading of the selected out-of-range laboratory parameters (see Appendix B).

A laboratory result that is out-of-range but below Grade 2 does not qualify as an AE to be recorded, and does not require determination of clinical significance or relatedness. A result will be checked as not clinically significant "NCS" if it is outside the lab range but does not rise to a Grade 2 on the AE Table.

Serology for Chronic Viral Hepatitis Infections **(PHASE 2 ONLY)**

Blood specimens will be evaluated for the following using tests qualified in Vietnam:

- Hepatitis B virus surface antigen (HBsAg)
- HCV antibody using anti-HCV test

Specimen collection will occur on Day S1. Determinant results of a subject's testing must be obtained from the laboratory prior to administration of any study product.

Pregnancy Test

In order to confirm pregnancy status of females who are able to become pregnant, a qualitative human chorionic gonadotropin (hCG) test will be done on a urine sample.

Pregnancy testing will be done on fertile women on Days S1, S2/D1, and D22. No injection of study product may be given to a fertile woman without a pregnancy test being done or to any woman with a positive pregnancy test.

Clinical Safety Laboratory Tests for Screening and Follow up **(PHASE 2 SUBJECTS ONLY)**

To monitor potential vaccine toxicity for PHASE 2 SUBJECTS ONLY, blood specimens (fasting not required) will be collected at screening on Day S1, Day 8, Day 22, and Day 29 and evaluated for the following using tests qualified in Vietnam.

- Creatinine
- Alanine aminotransferase (ALT)
- Total bilirubin
- Total protein
- Number of WBC
- Hemoglobin content (Hgb)
- Platelet count

8.2.2 Immunological Assays

Serum Antibody to Influenza Virus Detected by HAI

The HAI assay is the most frequently used serologic test for determining immunologic response to influenza vaccination. Serum specimens will be tested for the presence of HAI antibodies to influenza by the National Institute of Hygiene and Epidemiology (NIHE), in Vietnam. Briefly, sera are pretreated with heat and a receptor-destroying enzyme to reduce non-specific inhibition. In 96-well micro titer plates, serum specimens are then serially diluted using 2-fold dilutions and incubated with standardized titers (typically 4 AU) of influenza virus antigens representing vaccine strain. After incubation, red blood cells (RBC) are added to individual wells and allowed to sediment. Plates are tipped, and RBCs that have settled will produce a streak (RBCs run or flow), indicating inhibition of hemagglutination and the presence of serum antibodies against the influenza test strain. Wells with lattice formation (hemagglutination) will not streak. When processing paired sera (pre- and post-vaccination), an increase in antibody titer indicates response to vaccination. The choice of RBC is particularly important for detecting antibodies to A/H5N1 virus. Chicken RBCs which are typically used in HAI assays are not very sensitive to H5N1 and should not be used. Instead, horse-derived RBCs are preferred and will be utilized after appropriate screening of horse donors. If no suitable donor is available, RBC from turkey may also be used in this assay.

The HAI assay will be conducted in serum samples from all the subjects in Phase 2 of the study and in a subset of approximately 300 subjects receiving the IVACFLU-A/H5N1 (vaccinees) from one study site in Phase 3. For this assay, serum specimen collection will occur on Days 1, 22 (Phase 2 only), and 43. On Days 1 and 22, collection must take place prior to administration of the study product.

Serum Antibody to Influenza Virus Detected by Microneutralization Assay (MNT)

The microneutralization assay is an alternative test for determining immunologic response to vaccination. It is a highly sensitive assay that can provide information on the ability of induced antibody to neutralize influenza virus. NIHE will test serum specimens for the presence of neutralizing antibodies to influenza by microneutralization. For this assay, serial dilutions of serum and fixed amount of live influenza vaccine virus are added to a culture of Madin-Darby Canine Kidney (MDCK) cells. Virus-infecting cells will produce a cytopathic effect that can be detected by staining. Titers of neutralizing antibodies are expressed as the amount of the greatest dilution of serum giving a neutralization of 50% of tissue cytopathic effects of the virus in the tissue culture ($TCID_{50}$).

The MN assay will be conducted in all subjects in Phase 2. If the results from Phase 2 suggest that MN testing would add value to the study, a decision will be made to conduct the MN in the Phase 3 study. For

this assay, serum specimen collection will occur on Days 1, 22 (Phase 2 only) and 43. On Days 1 and 22 collection must take place prior to administration of study product.

The table below summarizes the number of subjects enrolled and bled for serology in the Phase 2 and Phase 3 components of the study.

		Phase 2	Phase 3
	Number (No.) of study sites	1	3
	No. of sites taking blood for serology	1	1
	No. of Subjects (total)	300	1500
Vaccine Group	No. of subjects injected	200	1000
	No. of subjects bled	200	333
	No. tested by HAI	200	333
	No. tested by MN	200	TBD
Placebo Group	No. of subjects injected	100	500
	No. of subjects bled	100	167
	No. tested by HAI	100	167
	No. tested by MN	100	TBD

TBD = to be determined based on the phase 2 serology results

8.2.3 Preparation, Processing, and Transport of Specimens

Blood Specimens

Blood will be collected for testing in multiple assays for the following: selected hematology and chemistry tests, HBV and HCV serology, HAI antibody serology, and neutralizing antibody serology.

Collection of Blood

Following universal precautions, blood will be collected from the forearm by venipuncture into vacutainer tubes or regular tubes. Blood for chemistry, serology for chronic viral hepatitis infections, and serology for anti-influenza antibodies must be collected in tubes appropriate for collection of serum (serum separator tubes). Blood for hematology must be collected in tubes appropriate for collection of whole blood (tubes containing potassium EDTA or appropriate anti-coagulant). Blood for hematology should be transported to Nha Trang Pasteur Institute lab within 4 hours for further processing. Volumes of blood required for the different categories of assays at different time-points are shown in the table below.

Test	Collection tube	Blood volume (mL)	S1	D1	D8	D22 prevac	D29	D43
Whole blood for hematology*	Anticoagulant	2	✓		✓	✓	✓	
Biochemistry, HBV & HCV testing*	Serum separator	3	✓		✓	✓	✓	
Anti-influenza serologic assays#	Serum separator	5		✓		✓*		✓
Total volume: Phase 2			5 mL	5 mL	5 mL	10 mL	5 mL	5 mL
Total volume: Phase 3			0	5 mL	0	0	0	5 mL
*Phase 2 subjects only; # On all Phase 2 subjects and a subset (HAI = approx. 300 vaccinees; MN = to be determined) of Phase 3 subjects								

(The total volume of blood planned to be collected from each Phase 2 subject during the course of the study will be less than 35 mLs, unless a re-draw is required. The total volume for Phase 3 per subject is not more than 10 mL, unless a re-draw is required.)

Processing of Whole Blood for Hematological Parameters

Immediately after collection, the blood specimen tube will be gently inverted 4 or 5 times, (labeled with the subject's study participant number, the collection date, and the blood specimen number), and submitted within 4 hours to the laboratory for processing. Whole blood for hematology will not be divided.

Processing of Sera for Biochemical and Hepatitis Virus Testing

Immediately after collection, the blood specimen tube will be stood upright to clot for at least 30 minutes at room temperature before transport to the laboratory for processing.

Division of Sera

Serum specimens for anti-influenza serologic assays will be divided. Specimen division should be performed for only one participant at a time to avoid mixing blood tubes. The procedure should be carried out as follows:

- After centrifugation, the person in charge of dividing specimens should carry out the operation by taking the tubes one by one from the centrifuge.
- The operator will only place in a rack the number of tubes (four) necessary for the division of one subject's specific blood specimen and will affix the completed labels onto the tubes checking the study participant number, collection date, and blood specimen number.
- Each serum specimen will be divided into 4 aliquots as follows:
  - 1st aliquot: 0.6 mL for HAI assays
  - 2nd aliquot: 0.6 mL for microneutralization assays
  - 3rd aliquot: 0.6 mL as first back-up
  - 4th aliquot: remaining serum as second backup

- The study participant number, date of collection, blood specimen number, number of divisions obtained, and the date and time of division will be specified on a serologic specimen log form. On this form, comments may be made on the quality of specimens (e.g., hemolyzed, contaminated, etc.).

Conditions for Transport and Storage of Sera

Serum specimens for anti-influenza serologic assays will be immediately frozen to –20˚C after division and stored at this temperature until use. All handling will be done to prevent unnecessary freeze-thaw cycles (i.e., back-up samples should not be thawed unless required for testing). Temperature monitoring will be done to assure maintenance of cold chain and specimen quality.

Urine Specimens

Urine will be collected on fertile women for pregnancy testing on visits S1, S2/D1, and D22. No urine specimens will be stored after testing.

9 Assessment of Safety and Adverse Events

9.1 Specification of Safety Parameters

The safety profile will be evaluated by the proportion of subjects experiencing AEs, related or not related, under the following five categories:

- Number and percentage of subjects with solicited local and systemic adverse events within 30 minutes after each vaccination.
- Number and percentage of subjects with solicited local adverse events (redness, swelling, pain, induration, and tenderness) over the 7-day period (Days 1-7) post vaccination.
- Number and percentage of subjects with solicited systemic adverse events (fever, fatigue/malaise, generalized muscle aches, joint aches, chills, nausea, vomiting, and headache) over the 7-day period (Days 1-7) post vaccination.
- Number and percentage of subjects with unsolicited adverse events for 21 days post each vaccination. (Unsolicited adverse events are any untoward medical occurrence in the subject, temporally related to receipt of the study products, whether or not considered related.)
- All serious adverse events (SAEs) occurring over the entire study period (Day 91).

9.2 Methods and Timing for Assessing and Recording Safety Parameters

9.2.1 Adverse Events

An AE is defined as any untoward medical occurrence in a patient or clinical investigation participant administered a pharmaceutical product, which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product,

whether or not considered related to the medicinal product. Information to be collected on AEs includes event description, time of onset, clinician's assessment of severity, relationship to study product, and time of resolution/stabilization of the event. AE assessment should be made only by those with the training and authority to make a diagnosis.

In this protocol, laboratory results are considered AEs when the result is Grade 2 or above.

Any medical condition that was present at the time that the subject was enrolled should not be reported as an AE, but should be reported as a pre-existing condition on the Medical History Form. However, if this condition occurs with greater frequency or severity during the study, it should be recorded as an AE.

AEs, including laboratory abnormalities that are Grade 2 and above, should always be assessed for severity and relationship to study products.

This study will collect and record solicited local and systemic reactogenicity and unsolicited AEs. For clarity, solicited reactogenicity refers to AEs specifically asked about during the 7-day post-vaccination period. Unsolicited events are those not specifically solicited, but may be reported by the subject at any time or observed by study staff while the subject is at a clinic for a study visit. If a new solicited event is reported by the subject outside of the 7-day post-vaccination window, this event will be recorded as an "unsolicited AE" because it will be outside of the 7-day window for collection of solicited reactogenicity.

SAEs are defined in Section 9.2.8.

9.2.2 Severity of Event

All AEs, including clinical laboratory test results Grade 2 and above, will be assessed by a study clinician to quantify severity using a protocol-defined grading system. This study will use the Toxicity Table for Grading Adverse Events (see Toxicity Table in appendix). For events not included on the table, the following guidelines will be used to quantify intensity:

Grade	Description for grading when an event is not on Toxicity Table
1 (Mild)	Events require minimal or no treatment and did not interfere with the subject's daily activities.
2 (Moderate)	Events resulted in a low level of inconvenience or concern to the subject with therapeutic methods. Moderate events might cause some interference with functioning.
3 (Severe)	Events interrupt the subject's functioning and might require systemic drug therapy or other treatment. Severe events are usually incapacitating.
4 (Life threatening)	Any adverse experience that places the subject, in the view of the investigator, at immediate risk of death *as it occurred* (The investigator should *not* grade a reaction as life-threatening that had it occurred in a more severe form, might have caused death).
Basic Self-Care Functions – Adult: Activities such as bathing, dressing, toileting, transfer/movement, continence, and feeding.	

Usual Social & Functional Activities – Adult: Adaptive tasks and desirable activities, such as going to work, shopping, cooking, use of transportation, pursuing a hobby, etc.

Changes in Severity of an Event

Changes in the severity of an AE should be documented to allow an assessment of the duration of the event at each level of intensity to be performed. AEs characterized as intermittent require documentation of onset and duration of each episode.

9.2.3 Relationship to Study Vaccines

The clinician's assessment of an AE's relationship to study product is part of the documentation process. The clinician must determine whether there is a reasonable possibility that the investigational product(s) caused or contributed to an AE. It is essential to have the best assessment possible as to whether adverse events are related to investigational products.

The relationship assessment, based on clinical judgment, should rely on the following:

- Temporal (time-based) relationship between the event and administration of the investigational product.
- Plausible biological mechanism for the investigational product to cause the AE.
- Possible alternative etiology for the AE.
- Previous reports of similar AEs associated with the investigational product or other vaccines in the same class.

To help assess, the following guidelines will be used:

Related – There is a reasonable possibility that the study vaccine caused the AE. "Reasonable possibility" means that there is evidence to suggest a causal relationship between the study product and the AE.

Not Related – There is not a reasonable possibility that the administration of the study product caused the event.

Any solicited local or systemic reactogenicity that occurs during the 7-day period post-injection is automatically regarded as related.

9.2.4 Guidelines for AEs

To improve the quality and precision of acquired AE data, the PI should observe the following guidelines:

- Whenever possible, use recognized medical terms when recording AEs on the AE CRF. Do not use colloquialisms and/or abbreviations.
- If known, record the diagnosis (i.e., disease or syndrome) rather than component signs, symptoms, and laboratory values on the AE CRF (e.g., record congestive heart failure rather than

dyspnea, rales, and cyanosis). However, signs and symptoms that are considered unrelated to an encountered syndrome or disease should be recorded as individual AEs on the CRF (e.g., if congestive heart failure and severe headache are observed at the same time, each event should be recorded as an individual AE).

- AEs occurring secondary to other events (e.g., sequelae) should be identified by the primary cause. A "primary" AE, if clearly identifiable, generally represents the most accurate clinical term to record on the AE CRF. If a primary serious AE (SAE) is recorded on an SAE CRF, events occurring secondary to the primary event should be described in the narrative description of the case.

  For example:

Orthostatic hypotension	→	Fainting and fall to floor	→	Head trauma	→	Neck pain

  The primary AE is orthostatic hypotension.

- Out of range laboratory results that are Grade 2 or higher will be considered AEs and should be entered onto an AE form.
- Death is an outcome of an event. The event that resulted in the death should be recorded and reported on the SAE CRF.
- For hospitalizations related to surgical or diagnostic procedures, the illness leading to the surgical or diagnostic procedure should be recorded as the SAE rather than the procedure itself. The procedure should be recorded in the case narrative as part of the action taken in response to the illness.
- Pregnancies are not considered AEs. They will be recorded on a separate Pregnancy CRF. Pregnancy outcomes that include stillbirth and any congenital anomalies must be reported as SAEs.

9.2.5 Solicited Reactogenicity (Expected Reactions)

Assessment of 30-minute Reactogenicity

The 30-minute Reactogenicity is assessed 30 minutes after vaccination on Day 1 and Day 22. The 30-minute Reactogenicity Assessment consists of inspection of the upper arms for presence or absence of redness, swelling, hardness, pain, or tenderness; documentation of the presence or absence of headache, fever, fatigue/malaise, muscle aches, joint aches, nausea, vomiting, and chills.

Appropriate medical treatment must be readily available in case of an anaphylactic reaction following the administration of the study product. Immediate reactions will be assessed by a study physician or appropriately trained medical staff. All reactions that occur during this time will be recorded on the CRF. Any immediate reaction which meets the criteria for an SAE must also be documented on an SAE form.

Emergency medicine will be available at the study clinic in the event there are any adverse reactions or events occurring among subjects participating in this research. If anaphylaxis occurs after vaccination, it

must be treated in accordance with Decision No. 08/1999-TT-BYT, dated 04 May 1999. Treatment for mild reactions after vaccination will be per "Guidance on the treatment of post- injection reactions" of the National Expanded Program on Immunization. The applied treatment methods must be recorded and kept in the subject file.

9.2.6 Solicited Local and Systemic Reactions

Specific local and systemic reactions will be solicited (specifically asked of subjects) while subjects are in the study. These specific reactions, which are signs and symptoms, will be graded by a study clinician using the Toxicity Table for Grading Adverse Events (see Toxicity Table in Appendix B). Grading will use predefined scales based on functional assessment or magnitude of reaction, where available. Where grading scales are not provided, the reaction will be graded for severity based on interference with subject functionally, as for all other AEs (see Section 9.2.1). Severity of redness, swelling, and induration at the injection site should always be graded based on size.

Local Reactions:

- Size of redness (at site of injection) in cm
- Size of swelling (at site of injection) in cm
- Size of induration (hardness at site of injection) in cm
- Pain (at site of injection)
- Tenderness (at site of injection)

Systemic Reactions:

- Fever/body temperature (and body location of measurement)
- Fatigue/malaise
- Generalized muscle aches
- Joint aches/pains
- Chills
- Nausea
- Vomiting
- Headache

Solicited Local and Systemic Reactogenicity will be collected through study Day 7. If a solicited sign or symptom has started during the 7 days post vaccination and continues beyond the 7 days, it will continue to be reported as a reactogenicity symptom. Any solicited sign or symptom starting after 7 days post vaccination will be recorded as an “unsolicited AE”.

9.2.7 Unsolicited Adverse Events

Unsolicited adverse events are any AEs that occur any time after the vaccine/placebo is given (temporally related to study product), whether or not deemed "related" to the product, and are not solicited (specifically asked of the subject). Unsolicited AEs can be observed by study staff while the subject is at a clinic for a study visit or reported by the subject at any time. Any solicited sign or symptom starting after 7 days post vaccination will be recorded as an "unsolicited AE".

9.2.8 Serious Adverse Events

An SAE is defined as an AE that meets one of the following conditions:

- Death.
- Life-threatening (subject at immediate risk of death). *(This means that the subject was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe).*
- Requires inpatient hospitalization or prolongation of existing hospitalization.
- Results in congenital anomaly/birth defect. *(Only in the case of a woman becoming pregnant during the study period after administration of at least one injection of study product. All pregnancies must be followed to term and outcome reported to IVAC and regulatory agencies.)*
- Results in a persistent or significant disability or incapacity.
- Important medical events that might not result in death, be life-threatening, or require hospitalization might be considered SAEs when, based upon appropriate medical judgment, the event might jeopardize the well-being of the subject and require medical or surgical intervention to prevent one of the outcomes listed above. *(Medical and scientific judgment should be exercised in deciding whether reporting these events is appropriate.)*

All SAEs must be reviewed and evaluated by a study clinician (SAE relationship to study vaccine must be evaluated as outlined in Section 9.2.3) and recorded on an SAE form and reported, as specified in Section 9.3. All such SAEs should also be followed until satisfactory resolution or until the investigator deems the event to be chronic or the patient to be stable.

9.2.9 Procedures for Out-of-Range Laboratory Test Values

Out-of-range laboratory values and AEs:

To the extent possible, all reference ranges for clinical laboratory test results will be pre-specified. The site staff will follow the Toxicity Table for Grading Adverse Events (see Toxicity Table in Appendix B) for grading out-of-range laboratory results. Laboratory values that are out-of-range will not be considered an AE unless they qualify as a Grade 2 or above on the Toxicity Table. It is possible that a laboratory result will be out of the reference range for the laboratory, but not result in a grade on the Toxicity Table. In this case, no grading or reporting as an AE is required. The result will be coded as "ungradable."

Out-of-range test values may be considered an SAE if two circumstances are met:

1. The value rises to the level of Potentially Life-threatening (Grade 4), and
2. The event is determined by the Principal Investigator to pose an immediate risk of death.

A Grade 4 laboratory result does not, in and of itself, constitute an SAE. Grade 4 places a laboratory value as a potentially life-threatening event, but a Grade 4 laboratory result should not be reported as an SAE unless the PI has determined that it does, in fact, pose an immediate risk of death.

Assessing relatedness and clinical significance of out-of-range laboratory values:

All laboratory results should be reviewed within 36 hours of collection. Investigators should report any laboratory finding Grade 2 and above as an AE. Therefore, the investigator will assess relatedness and clinical significance for these findings.

Clinical judgment always should be used to determine whether a laboratory result requires additional follow up. However, the investigator should redraw any Grade 2 or above laboratory result that is deemed clinically significant at Day 8 at an unscheduled visit to check if the result has normalized.

Any Grade 2 or above laboratory value that is clinically significant and has not returned to normal should be marked by the investigators as “continuing” or “unresolved.” After termination of the trial, the investigator should assure that the subject is referred for appropriate medical follow-up, if indicated.

9.3 Reporting Procedures

9.3.1 Serious Adverse Events

All SAEs must be documented and reported to IVAC or its designate, even if the investigator considers that the SAE is not related to treatment. The study clinician will complete a **Serious Adverse Event Form** within the following timelines of such events:

- All deaths and immediately life-threatening events, whether related or unrelated, will be recorded on the Serious Adverse Event Form and sent by fax or email within 24 hours of site awareness.
- SAEs other than death and immediately life-threatening events (i.e., events resulting in hospitalization or prolongation of hospitalization, persistent or significant disability or incapacity, or other significant events determined by the investigator to be SAEs), regardless of relationship, will be reported via fax or email by the site within 48 hours of becoming aware of the event.

IVAC will be primarily responsible for medical monitoring of serious adverse events documented by the investigator. Medical Officers from PATH serving as technical consultants will review all serious adverse events and provide guidance regarding SAE management, including classification and reporting. Details for review of serious adverse events and other unanticipated problems will be in an SOP drafted prior to study initiation.

9.3.2 Reporting of AEs

Collected SAEs and AEs will be reported to responsible ethical review committees according to their

requested timelines. An SOP for reporting to the responsible committees will be developed with reporting requirements and timelines prior to study initiation. It will be the investigator's responsibility to assure that all reportable events are reported to the proper authority, or to IVAC, and/or its designate in a timely manner and according to existing SOP. PATH technical consultants may assist the investigator with regulatory reporting, per the finalized SOP.

9.3.3 Other Unexpected Issues/Unanticipated Problems

During study process, if there are any problems related to the trial (unanticipated problems), the Principal Investigator is responsible for reporting to IVAC and PATH to discuss reasonable ways of handling the problem. The Principal Investigator is responsible for reporting any unanticipated problems that affect the health, welfare, or rights of study participants, or that may impact the integrity of the study data to the ethics committees involved in the review of the research. The Principal Investigator should maintain written documentation of all unanticipated problems, their reporting, and resolution.

9.3.4 Reporting of Pregnancy

All pregnancies detected among women enrolled in the trial who receive at least one injection of study product must be reported on a pregnancy report CRF. All pregnancies must be followed to term and outcome reported to IVAC and regulatory agencies. Unblinding of allocation of treatment of female subjects who become pregnant will not occur until after study completion, unless medically indicated.

9.4 Duration of Follow Up for AE Resolution

All reported AEs should be followed until resolution or stabilization, or until the subject's participation in the study ends. Subjects who have an ongoing study product-related SAE at study completion or at discontinuation from the study will be followed by the PI, or his/her designee, until the event is resolved or determined to be irreversible, chronic, or stable by the PI.

9.5 Safety Oversight

9.5.1 Protocol Safety Review Team

Safety will be monitored daily during the active immunization Phase of the study by on site clinical staff, and routinely by the Medical Officer at PATH and designated pharmacovigilance medical officer from a CRO.

9.5.2 Data and Safety Monitoring Board

A DSMB comprised of independent vaccine and infectious diseases experts and a biostatistician will (1) review the initial cohort of trial participants and advise on continuing with vaccinations for the rest of the study and (2) periodically review cumulative data. To allow for accurate assessment, the DSMB will

review reports that have been unblinded to the study code. Investigators and other persons associated with the conduct trial will remain blinded.

Initial Cohort Review:

After 300 subjects receive both vaccinations, further enrollment in the study will pause for approximately 6 months while the immunogenicity and safety data are compiled by the Data Management CRO and reviewed by the DSMB. Study enrollment will proceed if the DSMB advises continuation of the trial and the Vietnam Ministry of Health concurs.

Periodic Review:

The DSMB will conduct periodic review of (but will not be limited to): demographic information on study; interim/cumulative data for evidence of study-related AEs; discontinuations of study vaccinations; data quality, completeness, and timeliness; factors that might affect the study outcome or compromise the confidentiality of the trial data (such as treatment and endpoint unblinding); and, factors external to the study such as scientific or therapeutic developments that may impact participant safety or the ethics of the study.

The DSMB reviews will be summarized and contain recommendations to the study sponsor concerning whether or not there are safety concerns, if the study should continue without change or modified, or if it should be terminated. Decisions regarding permanent discontinuation of study product in individuals will be made by the PSRT based on careful review of all relevant data and by consulting with the DSMB, if necessary. Although it is not likely to happen, if the protocol team has serious safety concerns with the study and concludes the study product should no longer be administered and accrual into the protocol should stop, the team should request a review of the data by the DSMB. If, at any time, a decision is made to discontinue the study product for all participants, IVAC will notify the MOH and the site investigators of record will notify the responsible IRBs/IECs expeditiously.

DSMB recommendations will be carefully considered by the sponsor. If a disagreement arises between the sponsor and the DSMB, the sponsor will discuss it with the DSMB in order to reach consensus. If attempts to reach consensus fail, the sponsor's opinion will prevail. In such situation, the sponsor will inform the regulatory authorities.

All summary reports from the DSMB will be submitted to IRBs.

10 Monitoring

10.1 Monitoring Plan

Individuals qualified by education, training, and experience will carefully monitor the study. The study monitors will periodically contact the site and perform on-site visits. The extent, nature, and frequency of visits will be based on such considerations as study objectives, study design and complexity, and enrollment rate. Periodicity and nature of monitoring activities will be described in the Monitoring Plan that will be approved by IVAC in advance of monitoring. The Monitoring Plan will contain detailed

report requirements and study progress for IVAC. Representatives of IVAC or designates may participate in monitoring visits or visit the study site on their own in order to provide proper oversight.

10.2 Initiation Visit

The study monitor will contact the site prior to the start of the study to discuss the protocol and data collection procedures with site personnel. Prior to enrollment of subjects at the study site, specific regulatory documents must be available. These include approvals from the independent ethics committee (IEC) at the Vietnam Ministry of Health and from institutional review boards of the participating institutions. Curriculum vitae for key investigators must also be available. IVAC will inform the investigator of any additional documents that need to be provided.

10.3 Routine Monitoring Visits

Monitoring will be conducted according to an agreed upon Site Monitoring Plan. Monitoring will be targeted towards issues critical to the rights and welfare of study participants as well as accuracy and integrity of the study data. Individuals responsible for monitoring the study should have access to all records needed in order to periodically ensure the ethical and safe conduct of the study and the integrity/validity of the recorded data.

During sites visits and contacts, the monitor will:

1. Assess if consent was properly obtained.
2. Assess adherence to the protocol eligibility criteria.
3. Look for evidence that randomization was followed.
4. Look for evidence that blinding was maintained.
5. Look for evidence that the product was administered correctly.
6. Check on study conduct and documentation of procedures/assessments related to the study endpoints:
    - Specimens obtained correctly.
    - Specimens labeled correctly.
    - Reactogenicity diaries completed and collected.
7. Check on study conduct and documentation of protocol-required safety assessments, including SAEs.
8. Ensure that there is documentation of withdrawals and deaths with reasons provided.

As part of study conduct, the Principal Investigator agrees to allow the monitor direct access to all relevant documents and to allocate his/her time and the time of his/her staff to discuss findings and relevant issues. The study consent also makes participants aware that medical records relevant to events in the study may be accessed and viewed by people conducting and overseeing the study.

The Principal Investigator also agrees to allow representatives of IVAC or its designates to occasionally accompany the monitor during site visits.

10.4 Close-out Visit

Upon completion of the study, the study monitor and the investigator will conduct the following activities:

- Data clarification and/or resolution.
- Accounting, reconciliation, and destruction at sites of used and unused vaccines.
- Review of site study records for completeness.
- Return of all study data to IVAC.

11 Audits and Inspections

For the purpose of compliance with applicable regulatory guidelines, it might be necessary for IVAC, it's designates, or national or foreign regulatory authorities to conduct a site audit. This could occur at any time from site initiation to after conclusion of the study.

The Principal Investigator agrees to allow the auditor to have direct access to all relevant documents and to allocate his/her time and the time of his/her staff to the auditor to discuss findings and any relevant issues.

National and foreign regulatory authorities may conduct a regulatory inspection of this study. If a regulatory authority requests an inspection, the Principal Investigator must inform IVAC immediately about this request. The Principal Investigator agrees to allow the inspector(s) direct access to all relevant documents and to allocate his/her time and the time of his/her staff to the inspector(s) to discuss findings and any relevant issues.

12 Statistical Considerations

12.1 Study Hypothesis

The study hypothesis is that two 0.5 mL doses of whole virion monovalent A/H5N1 influenza vaccine (IVACFLU-A/H5N1) adjuvanted with alum will be safe and well tolerated in healthy adults, and that at least one of the two doses tested will be immunogenic in 60% or more of the subjects tested.

12.2 Sample Size Considerations

This is an operational, seamless Phase 2/3 trial with a primary objective to evaluate the immunogenicity and safety of two dose levels of IVACFLU-A/H5N1, 15 mcg vs. 30 mcg (study Phase 2), and select the optimal of the two doses to evaluate further for potential licensure (study Phase 3). The sample size for this study was selected for the primary immunogenicity analysis and the safety analysis to satisfy the licensure requirements by the MOH. The sample size for Phase 2 of the study is approximately 300 subjects (100 per group), and for Phase 3, 1500 subjects (1000 for the IVACFLU-A/H5N1 group and 500 for the placebo group).

Overall, a total of approximately 1100 subjects will receive the selected dose of study vaccine, which will allow for the recognition of SAEs occurring at a frequency of less than one percent. The probability of observing at least one vaccine-related serious adverse event among 1100 subjects is greater than 90 percent if the true rate of such events is 0.21 percent. If no vaccine-related serious adverse events are observed in 1100 vaccinees receiving IVACFLU-A/H5N1, this would represent an upper bound of the two-sided 95 percent Confidence Interval (CI) on the percentage of such events of 0.3 percent.

Sample Size	No. of Events	Exact Two-Sided 95% CI
N=1100	0 events	[0.0%, 0.33%]
	1 event	[<0.01%, 0.51%]
	2 events	[0.02%, 0.65%]
	5 events	[0.15%, 1.06%]
	10 events	[0.44%, 1.67%]

12.3 Immunogenicity

The sample size calculations for the primary immunogenicity endpoints for Phase 3 are based on the following acceptance criteria:

- Percentage of subjects achieving HAI titer ≥40 on 21 days post-dose two should meet or exceed 60%.

For the Phase 2 dose selection component (Phase 2), samples from approximately 100 subjects per IVACFLU-A/H5N1 dose level will be tested by HAI and MNT assay. Phase 2 of this study is designed to provide 80% power to detect a 20 percentage points difference in response rates between the two dose groups (e.g. 50% for the 15 mcg dose vs. 70% for the 30 mcg dose). The minimum statistical difference that can be detected at two-sided 5% alpha is approximately 14 percentage points between the two dose groups (e.g. 50% for the 15 mcg dose vs. 64% for the 30 mcg dose). The selection of the dose for the Phase 3 will be based on multiple immunogenicity endpoints as listed in the primary and secondary immunogenicity endpoints. The power calculations were estimated based on the two-sided 0.05 Z test with unpooled variance using PASS 13.

For the Phase 3 component, samples from approximately 300 subjects receiving the IVACFLU-A/H5N1 (vaccinees) will be tested by HAI for the analysis of the immunogenicity endpoint. MN testing for the Phase 3 will be determined based on the results from Phase 2 and a determination that MN testing will add value to the Phase 3 study. The table below provides exact two-sided 95% CIs for either endpoints for different observed response rates for 300 evaluable subjects. This study is designed to provide the precision of the immune responses as estimated by the width of the confidence intervals less than ±5.8 percentage points around the range of expected rates.

Observed Seroresponse Rate	Percentage of Subjects	Exact two-sided 95% CI
300/300	100%	[98.8%, 100%]
270/300	90.0%	[86.0%, 93.2%]
240/300	80.0%	[75.0%, 84.4%]
210/300	70.0%	[64.5%, 75.1%]

Observed Seroresponse Rate	Percentage of Subjects	Exact two-sided 95% CI
180/300	60.0%	[54.2%, 65.6%]
150/300	50.0%	[44.2%, 55.8%]

Also, this study with 300 evaluable subjects is designed to provide 97% and >99% probability to demonstrate adequate immune responses, ≥60% achieving post-dose two HAI titer 1:40, if the true percentages of subjects achieving seroprotective level are 65% and 70%, respectively.

12.4 Endpoints and Minimum Significant Differences

12.4.1 Definition of Analysis Sets

Definitions of Populations to be Analyzed:

Enrolled Population

All screened subjects who provide informed consent, regardless of the subject's randomization and treatment status in the trial.

Full Analysis (FA) Population

All subjects in the enrolled population who were randomized, received a study vaccination. This population will serve as the primary analysis population for all safety objectives. The analysis based on this population will serve as the supportive results for all immunogenicity objectives. Subjects will be analyzed as received.

Per Protocol (PP) Population

All subjects in the Full Analysis population who have valid post-vaccination immunogenicity measures with no major protocol violations that are determined to potentially interfere with the immunogenicity assessment of the study vaccine. This population will serve as the primary analysis population for all immunogenicity objectives.

The criteria for exclusion of subjects from the Per Protocol Population will be established before breaking the blind and will be based on the blinded review of protocol violations.

12.4.2 Analysis of Safety Endpoints

The safety profile of IVACFLU-A/H5N1 will be evaluated by the number and the proportion of subjects experiencing AEs, related or not related, of the following five categories for all subjects and by age group (18-40 years of age and 41-60 years age):

- Number and percentage of subjects with solicited local and systemic adverse events within 30 minutes after each vaccination.
- Number and percentages of subjects with solicited local adverse events (redness, swelling, pain, induration, and tenderness) over a 7-day period (Days 1-7; Days 22-28) post each vaccination.

- Number and percentages of subjects with solicited systemic/general adverse events (fever, fatigue/malaise, muscle aches (generalized), joint aches, chills, nausea, vomiting, and headache) over a 7-day period (Days 1-7; Days 22-28) post each vaccination.
- Number and percentages of subjects with unsolicited adverse events for 21 days post each vaccination.
- All serious adverse events (SAEs) occurring over the entire study period. (Days 1-91).

Counts of all events will be reported and summarized according to event severity as "any local AE", or "any systemic AE", and by relationship to administration of study product, as deemed by a blinded study clinician. Percentages of subjects experiencing each reaction or event, or at least one reaction or event, will be calculated along with two-sided exact 95% CIs. For the solicited local and systemic/general adverse events, Fisher's exact test for two proportions or Chi-squared test severity grade categories at 2-sided 0.05 alpha without a multiplicity adjustment will be used to compare the treatment groups as an initial screening step rather than formal statistical hypothesis testing for further clinical evaluation. No statistical testing will be performed for unsolicited AEs including SAEs.

12.4.3 Analysis of Immunogenicity Endpoints

Immune responses to IVACFLU-A/H5N1 will be evaluated by the following for all subjects in the immunology subset and by age group (18-40 years of age and 41-60 years age):

Phase 2 (all 300 subjects)

- Percentage of subjects with a serum HAI titer ≥ 1:40 on Day 22 and Day 43 **(Primary Endpoint)**.
- Percentage of subjects achieving a seroresponse (at least a four-fold increase in post-vaccination titer) on Day 22 and Day 43 as determined by HAI.
- Percentage of subjects with at least a four-fold rise in titer at Day 22 and 43, as determined by MN.
- Geometric Mean Titer (GMT) of Day 22 and Day 43 as determined by the HAI and MN tests.
- Geometric Mean Titer Ratio (GMTR) of Day 22/Day 1 and Day 43/Day 1 as determined by the HAI and MN tests.

Phase 3 (approximately 300 vaccinee subjects for HAI; MN testing to be determined on the results of Phase 2)

- Percentage of subjects with a serum HAI titer ≥ 1:40 on Day 43 **(Primary Endpoint)**.
- Percentage of subjects achieving a seroresponse (at least a four-fold increase in post-vaccination titer) on Day 43 as determined by HAI.
- Percentage of subjects with at least a four-fold rise in titer at Day 43, as determined by MN*.
- Geometric Mean Titer (GMT) of Day 43 as determined by the HAI and MN* tests.
- Geometric Mean Titer Ratio (GMTR) of Day 43/Day 1 as determined by the HAI and MN* tests.

* MN tests and associated endpoints will be conducted on Phase 3 vaccinees based on results from Phase 2 and a decision that MN testing will add value to the study.

Percentages of subjects with immune response will be calculated along the corresponding two-sided exact (Clopper-Pearson) binomial CIs. GMT and GMTR will be summarized by treatment group along with the corresponding two-sided 95% CIs, by exponentiating the corresponding log-transformed means and their 95% CIs. Titers below the lowest limit of quantitation (i.e., below the starting dilution of assay reported as "< 10") will be set to half that limit (i.e., 10 / 2 = 5). For Phase 2, two-sided 95% CIs for the difference in proportions of participants demonstrating seroresponse between the two dose groups will be based on the Newcombe hybrid score (METHOD=SCORE riskdiff-option for PROC FREQ in SAS). For the GMT and GMFR, two-sided 95% confidence intervals (95% CIs) for the ratios post-vaccination GMTs/GMFRs between two dose groups will be constructed using a log-normal distribution. The log values will be used to construct a 95% CI using t-distribution for the mean difference between the two treatment groups. Then the mean difference and the corresponding 95% CI limits will be exponentiated to obtain the GMT ratio and the corresponding CI. No comparisons will be made between the IVACFLU-A/H5N1 dose groups and the placebo group in both Phase 2 and Phase 3.

This study has a single primary endpoint and it maintains the experiment-wise Type I error rate at 2-sided of 0.05. No multiplicity adjustment to the error rate, alpha, will be made for secondary immunogenicity endpoints. Also no imputation of missing immunogenicity measures will be made.

13 Data Capture Methods

CRFs will be developed and data will be managed to the extent possible in accordance with internationally agreed-upon standards, such as the Clinical Data Acquisition Standards Harmonization, which defines basic standards for the collection of clinical trial data, and/or The Society for Clinical Data Management's Good Clinical Data Management Guidelines.

All the information required by the study protocol must be recorded on the CRF provided by the sponsor, or if it is laboratory assay data, transferred in a format agreeable to the sponsor. All data must be entered legibly, as described in any *CRF Completion Guidelines*. An explanation must be provided for any missing data. Data entered onto the CRFs must be accurate, legible, contemporaneous, original (or traceable to the original source), and attributable.

All source documents and CRFs should be completed in a neat, legible manner to ensure accurate interpretation of data. Black ink is required to ensure clarity of reproduced copies. When making changes or corrections, study staffs are to cross out the original entry with a single line, and initial and date the change. Do not erase, overwrite, or use correction fluid or tape on the original. All source documents and laboratory reports must be reviewed by the clinical and laboratory teams, who will ensure that they are accurate and complete.

The investigator must sign and date each CRF or batch of CRFs, attesting to his responsibility for the quality of all data recorded and that the data represent a complete and accurate record of each subject's participation in the study.

Clinical safety data will be entered onto study CRFs from laboratory report forms. Visit dates and laboratory procedure dates will be recorded on all forms. All participants will be assigned a unique

screening number and subject identification number at study enrollment – this study participant number will be included on all forms and in the trial database and will serve to link study data to specific individuals. CRFs will be entered, verified for accuracy, linked by study participant number, and managed using database management software with proper security, controls, and the ability to identify who is entering or making changes to the data in the system.

13.1 Database Management and Analysis Software

A detailed statistical analysis plan for preparation of the final study report will be created and made final prior to database lock and unblinding. All statistical analyses will be performed using SAS® software Version 9.2 or later.

Medical history and AEs will be coded using MedDRA dictionary Version 15.1. The frequency count and percentage of subjects will be summarized according to the coded terms of system organ class and preferred term. Subject-wise data listings will be provided.

13.2 Entering, Cleaning, and Management of the Database

Procedure of entering, cleansing, and management of the database will be developed and implemented by Contract Research Organization (CRO). CRO will perform data management, data analysis, and report writing. A Data Management Plan will be drafted by CRO and submitted to IVAC, PATH, and WHO to approval before implementation.

13.3 Potential Deviations and Method of Limiting Deviations

To limit the potential deviations, the trial uses the double blinded, randomized, and placebo-controlled study design.

To further limit the potential deviations, during the study process, the most critical study activities will be based on standard operation procedures (SOPs), particularly the activities related to the study record database, copying data from source documents, data entry, and the cleaning process. During the data entry process, the questionable, inappropriate data will be detected by the data management system developed by the CRO with data management responsibilities, and feedback will be given to clarify the questionable data via a data clarification form / DCF. All fixes on CRF must be signed by study staff and the fix date must be recorded.

14 Source Documents and Source Document Access

Prior to the start of the trial, the sponsor will determine which documents or data fields completed by the investigative team will be considered source documents and documented on a Source Documentation Table. Source documents for this study may be outpatient charts, inpatient charts, laboratory analysis forms, Diary Cards, and specimen collection logs. For some data fields, the CRF may be the source document. Data fields on the CRF for which there are separate primary source documents will be carefully completed using the named source document.

Only authorized study staff and representatives of IVAC and study monitors authorized by IVAC, PATH, overseeing ethical review committees, and regulatory agencies may have direct access to source documents containing study data. Subject identification will be revealed to authorized representatives of these organizations only when necessary.

15 Quality Control and Quality Assurance

15.1 General Considerations

The study will be conducted in accordance with the procedures specified in the protocol and staff will be guided by a study Manual of Procedures (MOP) or other written guidelines. Study data collection forms will be designed to guide staff on study conduct. Forms will also include areas for documenting that activities did, in fact, occur (even if these activities did not require recording of data) and that they are recorded in the appropriate sequence. All study staff must attend mandatory protocol implementation training prior to participant enrollment.

Individual SOPs will be developed and documented for key study procedures and refined/revised as necessary. These SOPs will be included in the study MOP at the site or in the laboratory.

Study data will be recorded on CRFs and then entered into the database throughout the study. After data has been entered, it will be checked systematically by data management staff according to a pre-specified data validation plan. Queries will be generated for site staff to clarify or correct throughout the study. Additionally, an audit trail will be kept of all changes to the data. All listings of the database will be reviewed and discussed for assessment of consistency and medical plausibility. After resolution of all issues, the database will be locked.

15.2 Trainings

Trainings for the research team (including the project manager, branch project manager, study coordinator, researchers, physicians, nurses, and technicians) participating in the clinical trial include: basics of research and ethics, information on how to conduct the trial, the SOPs to be used in the trial, and the procedures for drug management and use.

There will be two formal trainings before study initiation for all NIHE staff and doctors and nurses from nearby hospitals who will participate in the study. The first training course on good clinical practice (GCP) and ethics is expected to last three days. The second training will be related to the research protocol, SOPs, and implementing the study.

16 Ethics/Protection of Human Subjects

16.1 Ethical Standard

The study will be conducted in full conformity with the Vietnam GCP guidelines of MOH, No.12/2014/TT-BYT dated 20/03/2014, the Declaration of Helsinki, and all of the Vietnam MOH requirements and current laws in order to ensure the best protection for study subjects.

16.2 Study Risks and Benefits

16.2.1 Study Risks

Potential Risks to Participant Well-Being

The risks of the A/H5N1 vaccine are described in Section 2.3.

Besides administration of study product, collection of blood specimens may cause some discomfort to subjects. Venipuncture is sometimes associated with fainting, discomfort or pain, bleeding, bruising, redness, swelling, local hardness, and/or infection at the puncture site.

Study subjects will be observed closely by qualified clinicians and care, including emergency care that will be immediately available to subjects after vaccination, as needed. If additional urgent care or resources are needed, the subject will be transported to a local hospital. This hospital will be identified by the investigator prior to study initiation. The study will provide this care to the subject at no cost to the subject.

Medical care will be provided for participants in this study. This includes the following:

- Monitoring of subjects closely for 30 minutes after vaccination and providing emergency care for any immediate reactions.
- Monitoring of subjects for adverse events which are not life-threatening and providing care for at nearby local hospitals and treatment centers.
- Monitoring of subjects for severe adverse events and providing care at local hospitals and treatment centers.

I an adverse event occurs during the study period, IVAC will ensure coverage for the full cost of treatment according to the laws of Vietnam for research participants. The study site will establish an agreement with nearby medical centers to provide treatment at no cost to the participant for reactions that are not life-threatening, but nonetheless warrant medical observation or care.

Potential Risks to Participant Privacy

Personal identifiers, including name, birth date, sex, and location/address of residence will be collected and recorded on some study data collection forms. As a result, a potential risk of “loss of confidentiality” exists. To avoid this risk, subjects will be assigned a unique study participant number that will be used to identify the participant and link, using a master linking document, an individual to his/her study data and/or biological specimens. Whenever feasible, use of identifiers will be avoided and the unique study

participant numbers will be used instead. Case report forms (CRF) to be sent to the CRO selected for data management and will contain only unique study participant numbers to identify the participant. Paper-based records will be kept in a secure location and only be accessible to authorized personnel involved in the study. Computer-based files will only be made available to personnel involved in the study through the use of access privileges and passwords. Individual participants will not be identified in any study related reports. Study staff will treat all study data, including subject identifiers and laboratory testing results, as confidential and not to be shared with anyone unauthorized to view such data.

Biological specimens will be identified by study participant number; no personal identifiers will be utilized on any biological specimen. Likewise, laboratory reports will utilize only study participant numbers. Biological specimens will be stored in the laboratories of NIHE where biological specimens will be tested using assays specified in this study protocol. There may be testing outside of Vietnam at a facility that will use the specimens to provide technical assistance to NIHE. The specimens will continue to have no personal identifiers even if they are stored at another laboratory.

16.3 Potential Benefits

Direct benefit to study participants from vaccination, i.e., protection from A/H5N1 influenza, is unclear, but a possible benefit.

Potential subjects will have aspects of their health status screened by qualified clinicians and through laboratory testing. This screening will be free of cost to the subject and may provide important health information to the screening candidates. Screening laboratory tests will be offered to all people who present for screening, even those who may screen out based on medical history and physical exam. Results will be reviewed with them and shared with their personal physician if the person indicates on the screening consent that this is desired. If the participant agrees to share their results with their personal physician, the study staff should obtain the contact information of the personal physician.

Subjects may not benefit personally through study participation.

17 Financing and Insurance

The WHO will fund this trial. Any financial engagement with the clinical study site, NIHE, will be regulated by a separate agreement. Financing of the study by WHO may be disclosed to study subjects in the ICFs.

IVAC will maintain the product liability insurance to cover treatment for study related injuries. IVAC will also maintain employer liability insurance or shall self-insure, as necessary, to meet its liability obligations under this protocol as well as sufficient levels of all legally mandated insurance, including at a minimum: professional liability coverage for the investigator, trial team, and all other employees, contractors, and agents providing services to this trial. As applicable, IVAC will maintain insurance to cover any general liability and product liability to meet its obligations under Vietnam law.

18 Assurance of Emergency Medical Care and Care for Other Adverse Events

Study subjects will be observed by qualified clinicians after each vaccination, and emergency care will be immediately available to subjects who need it. If additional urgent care or resources are needed, depending on each case, the subject will be provided urgent care and transported to a hospital. Signed agreements between study investigators and officials at hospitals near each study site will be in place to assure admittance of those with severe or life threatening side effects requiring urgent or supportive care. The study will provide this care to the subject at no cost to the subject.

Most adverse events that are expected and non-emergent can be handled at the study site by the clinical staff as they occur at no cost to the participant. These would be events such as fainting, lightheadedness, bruising or swelling from the injection of the study products or blood draws, etc.

19 Institutional Review Boards and Independent Ethics Committee

There are several Institutional Review Boards and Independent Ethics Committees reviewing this study because of the various collaborations and funding mechanisms of the institutions involved. The PATH Research Ethics Committee has an authorization agreement with the WHO Ethics Research Committee (WHO ERC) for review of the research. WHO ERC is reviewing the study based on WHO funding of the research. In addition, NIHE will have an independent ethics committee review.

No human subject research activities will be conducted without the review and approval of all relevant ethics committees of the entities involved in the study. The protocol and all amendments will have initial and continuing review and approval by an independent ethics committee (IEC) responsible for clinical trials in Vietnam. This IEC is the Vietnam MOH Ethics Committee, which is the ultimate authority for decisions related to this trial. The MOH will acknowledge the review by participating institutions' IRBs designed to ensure that their staff meet their responsibilities in conducting human subjects research. In Vietnam, the investigator is responsible for completing and submitting the clinical trial application documents to the MOH for review.

NIHE maintains an institutional review board. This study will be reviewed and approved by NIHE IRB prior to submission of Vietnam MOH IEC. All amendments will be approved by Vietnam MOH IEC before implementation, as appropriate.

The PI or designate shall maintain copies of all application documents and forward copies of all IRB and IEC documents and approvals prior to the start of the study. The approval letters must identify all documents approved and list the study site, study investigator, protocol title, version number, and date. Date and number of the ICF as well as the date of IRB or IEC approval must also be included in approval letters. The PI will sign all approved versions of the protocol.

The investigator is responsible for notifying the IEC and all IRBs of problems related to risks for participants, according to the requirements of the IEC and each IRB.

The investigator may not change or deviate from the protocol without prior written IRB/ IEC approval of appropriate amendments, except when necessary to eliminate immediate hazards to the subjects or when the changes involve only logistical or administrative aspects of the study (e.g., change of telephone number, etc.).

IVAC will report to the MOH and the IEC/IRBs any new information related to the study vaccine which possibly affects the safety of subjects or their risk/benefit ratio for participating in this trial. Any safety support means taken must be reported to the authorities. Reports on the implementation of projects are to be periodically submitted to the Ethics Committee of the MOH.

The investigator will be responsible for reporting to the MOH and the IEC/IRBs when the clinical study has been completed. This must occur within 90 days after the end of experimental phase of the study (i.e., involvement of human subjects in any study procedure). If the clinical study is terminated earlier than planned, the notice must be submitted within 15 days and reasons must be clearly explained.

20 Media Planning for the Community

Before conducting the study, a risk media plan will be developed between WHO, IVAC, and NIHE in case there is media interest in the study. This plan will address issues such as who are appropriate contacts for each of the trial partners in case of contact by the media; identification of appropriate spokesperson for each entity; and an Internal Q&A on the vaccine candidate, trial, partner(s), project, and other issues as necessary.

21 Informed Consent Process

A clinical trial involving human subjects cannot be conducted until the following factors have been fully met:

1. IEC/IRBs concludes that risk/benefit ratio is favorable.
2. Subject signs the written informed consent to participate in research.
3. Investigator provides complete information on the clinical trial to the subject and has answered the subjects questions to the satisfaction of the subject.
4. There is a commitment to respect the individual subject’s freedom and confidential information as well as the subject's physical and mental security.
5. A provision is made for health care for all subjects in the case of adverse events related to the trial or study vaccine.
6. Subjects are provided full contact information of the investigator should the subject request more information or need to report any health concerns he/she may have during the trial.

The following issues must be included in discussions with potential participants prior to obtaining their informed consent to participate in the study:

- The purpose of research, time duration that subjects need to participate, procedures involved in the study, scientific evidence that justifies conducting this experimental trial in humans, and the potential risks and known benefits of participating in the research.
- Randomization and what chances the subjects have of receiving the study vaccine or placebo.
- That study staff will not know which study product (vaccine or placebo) the subject will receive and that the study staff and subject will have no way to choose which product is received by the subject.

- That the subject's participation is voluntary and refusal to participate will not result in any fine, loss of rights, or access to medical care that the subject is normally entitled receive.
- In the event of unforeseen circumstances or needs, the investigator may decide to withdraw the subject from continued participation in the research, even without the consent of the subject.
- That the subject will be provided with the results of any new important findings related to the trial or the study vaccine which may influence the subject's decision whether or not to continue participation in the research.
- The number of other subjects participating in the research.
- Who to notify as the point of contact with the investigator and IRBs in case the subject would like to know more information regarding the trial and his/her rights as research subjects.
- That the investigator is responsible for collecting signed and dated written informed consent forms from the subject regarding participation in the study before participation is allowed; that the subject will be given a signed and dated copy of the form to keep; and that the investigator must keep an original signed and dated copy of individual's signed and dated written informed consent form in the investigator's research files.

Written informed consent of the subject must be obtained before performing any trial procedures. Subjects will be made aware that authorized representatives of health agencies and IVAC will have access to their confidential medical information for the purposes of monitoring trial conduct or performing audits.

Written informed consent will be obtained from each subject in two-stages for Phase 2 subjects:

- Stage 1: A screening "ICF A" will be signed in duplicate on Day S1. This is because this study requires substantial clinical and laboratory screening of potential subjects prior to entry into the study and administration of Injection 1 of study vaccine or placebo. Only subjects who have passed the first day of screening (S1) will be invited to return to complete screening on Day S2.

- Stage 2: On Day S2/Day 1, after a subject is fully screened and eligibility is confirmed for entry into the trial in order to receive Injection 1 of study vaccine or placebo, the investigator must again review the full trial objectives and procedures as well as the possible risks, benefits, and alternatives. After this review, a separate vaccine study "ICF B" will be signed in duplicate. Only then may the subject be entered into the trial and allowed to undergo trial procedures.

Subjects in Phase 3 will sign one consent for screening and the study, because screening and enrollment can occur on the same day. ICFs will embody the elements of consent as described in the Declaration of Helsinki and the ICH Harmonized Tripartite Guidelines for Good Clinical Practice. Original ICFs must be kept on file by the investigator for possible inspection by regulatory authorities or IVAC. The subject must receive a copy (or second original) of the signed and dated ICF(s), and any subsequent updates or amendments to the ICF. The study monitor shall check the documentation of the individual ICFs during each monitoring visit.

Subjects will be informed that they will be compensated for their time and effort for participation in this trial, travel, and meals during study visits. For each study visit, each subject will be paid a set amount of 300,000 Vietnamese Dong that is the equivalent of about 13.5 US dollars.

22 Inclusion of Women, Minorities, and Children

Enrollment in this study is open to healthy adults of any gender and race or ethnicity who are able to read the study consent and complete the subject diaries. No person may be denied enrollment based on gender or race or ethnicity. However, the investigator should attempt to recruit equal numbers of men and women. The investigator may enroll different races and ethnicities in proportion to their presence in the local population; however, no special recruitment methods will be used to ensure certain levels of participation by any specific minorities residing in the source population. Enrollment will be closed when 1800 subjects (300 for Phase 2; 1500 for Phase 3) have been screened and determined eligible for entry into the trial.

The trial is open to adults 18 through 60 years of age only.

23 Subject Confidentiality

23.1 Confidentiality of Data

By signing the protocol, the Principal Investigator agrees that the study protocol, documentation, data, and all other information generated regarding the vaccines will be held in strict confidence. The investigator may divulge such information within regulatory restrictions and ethical considerations only to ethical review committees or similar expert boards or committees, and their affiliated institutions and employees, only under an appropriate understanding of confidentiality with such board or committee, and their affiliated institutions and employees. No information concerning the study or the data may be released to any unauthorized third party without prior written approval of IVAC. Any regulatory agency deemed appropriate, may consult study documents in order to verify CRF data. Investigators will ensure that all employees involved in the study respect the same rules.

Medical information about individual subjects obtained during the course of this study is confidential and may not be disclosed to third parties, except authorized monitors, auditors, or inspectors, or as a requirement by law. Confidentiality will be ensured by the use of study participant numbers for the identification of each subject; these study participant numbers will also be used for subject data in the subject files at the site and for the CRFs.

23.2 Confidentiality of Subject Records

Subject confidentiality is strictly held in trust by the participating investigators, their staff, and IVAC and their agents. This confidentiality is extended to cover testing of biological specimens in addition to the clinical information relating to participating subjects.

Study participants should not be identified by name on any data collection form or on any other documentation sent to IVAC and will not be reported by name in any report or publication resulting from data collected in this study.

Documents and data pertaining to the study will be kept in a locked room or in locked files under the responsibility of the Principal Investigator. IVAC will conduct periodic monitoring visits to ensure that

the data is stored securely. Only study clinicians and study staff will be granted access to the study data and records. Study data will be kept for 15 years after completion of the study, in compliance with Vietnamese law.

The investigators will keep individual data confidential to the extent permitted by law. Information will not be released to anyone other than the participant unless required to do so by law or directed by the participant (e.g., to release information to his or her health care provider).

24 Sharing of Study Results

24.1 Sharing of Study Results with the Subject

All results of clinical laboratory testing should be shared with each subject or made available for review by the subject. For the influenza immunologic results, the participant will be told that the results are not confirmed to provide protection against influenza A/H5N1, because the trial was not designed to answer that question; however, if he or she would like the results, the Principal Investigator will provide them.

When the clinical study report is completed, the investigator will share summary results (without any identifiers) with subjects via printed materials. These will be submitted for approval by all applicable ethics committees before distribution to study participants.

24.2 Sharing of Study Results with the Community

After the study results are approved by the Independent Ethic Committee of the Ministry of Health, a workshop will be organized to report the results at a national and local level with the participation of the sponsor, study group representatives, representatives of MOH, and the authorities and health officials of the provincial, district, and commune levels. The results of this study will later be published in peer-reviewed international and national scientific journals to share information with the international community.

25 Incidental Health Findings

The investigator may release subject clinical and clinical laboratory results data to the subject's primary care physician only if the subject agrees in writing to this action. The clinical staff will share and discuss any incidental health findings with the participant and help the participant seek proper medical follow-up.

26 Study Discontinuation

Study discontinuation is not expected to occur. However, if the study is discontinued for safety reasons, subjects will be informed of the reasons for discontinuation and of the implications/potential consequences for the subject.

27 Future Use of Stored Specimens

Biological specimens will be stored until the vaccine is approved (or for a period of for instance 5 years after the trial). This is to save sera in case additional questions may arise on the immunogenicity of the vaccine even after the study has been completed.

28 Data Handling and Record Keeping

28.1 Data Management Responsibilities

The investigator is responsible to ensure the accuracy, completeness, legibility, and timeliness of the data reported. Data collection is the responsibility of the clinical study staff at the site under the supervision of the primary investigator.

AEs must be graded, assessed for severity and causality (relatedness to study product), and reviewed by the primary investigator or designee. This must be completed as soon as possible to allow a realistic safety profile of the investigational product.

WHO will hire and oversee a data management contractor who will conduct data management activities for the trial. Analysis and reporting of the created study database will be done by the trial statistician at the Data Management CRO.

28.2 Planned Interim Analysis

The interim assessment will be performed when the safety and immunogenicity data through Day 43 visit is available for 300 subjects in the Phase 2 component. The purpose of this interim assessment is determined a dose to be studied in the Phase 3 component.

The interim assessment will be performed by a third party who is not involved in the conduct of the study. The unblinded results summarized by treatment group and the final decision will be submitted to the Vietnamese MOH for their review prior to the resumption of the enrollment. No individual listing will be generated. This interim assessment will not otherwise alter the course of the trial and blinded status of the study.

Since the purpose of this interim assessment is to select the dose for the Phase 3 component and the final confirmatory analysis will be solely based on the data generated for the Phase 3 component only, there is no need to make an adjustment to the Type I error rate.

28.3 Final Analysis Plan

The Final Analysis Plan will be the responsibility of the CRO, and detailed in the Data Management Plan. The Plan will be developed by CRO and submitted to IVAC, PATH, and WHO for approval before implementation. The database will be locked and the analysis will be conducted only after all data has been entered and cleaned.

28.4 Timing/Reports

It is estimated that the database lock will occur about 8 weeks after the final visit of the last study participant and the clinical study report should be completed within 6 months from the final visit of the last study participant.

28.5 Study Record Retention

Study data will be kept for 15 years after completion of the study. No records will be destroyed without the written consent of IVAC. It is the responsibility of IVAC to inform the PI when these documents no longer need to be retained.

29 Protocol Deviations

A protocol deviation is any noncompliance with the clinical study protocol, GCP, or site procedures. The noncompliance may be either on the part of the subject, the investigator, or the study site staff. As a result of any deviations, corrective actions are to be developed by the site and implemented promptly. Trial procedures shall not be changed without the consent of IVAC. Insignificant violations of the protocol will be examined on an individual basis taking into account recorded information for the reason(s) that the deviation occurred.

It is the responsibility of the site to use continuous vigilance to identify and report deviations to IVAC in a timely manner after identification. If required, reports of protocol deviations must be sent to the research ethics committees overseeing the research. The PI and his/her staff are responsible for knowing and adhering to their research ethics committee's/IRB's requirements.

30 Human Resources

30.1 Human Resource for the Study

The study research team will be qualified by experience, education, and training to conduct their responsibilities on this study.

The study site will make arrangements with local health centers to adequately care for participants who experience side effects/illnesses that need care beyond what the study site can provide.

The research team may use commune health centers to prepare a list for potential subjects, keep contact with study subjects, conduct non-vaccination follow up visits, and conduct home visits (if needed).

30.2 Training Plan

All key personnel (those responsible for the design and conduct of this study) will have completed Human Subjects Protection and/or GCP Training, as appropriate to their role, prior to interaction with any

participants or to having access to their confidential study data. In addition, staff will be trained on any written procedures that pertain to their role in the study.

31 Clinical Study Report and Publication Policy

31.1 Clinical Study Report

A Clinical Study Report (CSR) comprised of text and results tables reflecting all safety and immunogenicity data will be generated by IVAC or its designates. The CSR will be compliant with ICH E: 3 guidelines.

All data, documents, recordings, and information transferred to any contractor or obtained or prepared by any contractor, his consultants or persons associated by contractual relationships with any contractor during the trials, belong to IVAC.

All confidential information communicated to the Principal Investigator by IVAC shall be kept strictly confidential by him/her or any other person connected with the study and shall not be disclosed, either orally or in written form, by him/her or such person to any third party without prior written consent of the organization of which the information is the exclusive property.

Following completion of the clinical study report, the investigators, working with IVAC and representatives, are expected to publish the results, negative or positive, of this research in peer-reviewed scientific journal(s). IVAC may not prohibit the public dissemination of the results of this trial; details of the publication plan are specified in the Agreement between IVAC and NIHE.

31.2 Publication Policy

The International Committee of Medical Journal Editors (ICMJE) member journals have adopted a trials-registration policy as a condition for publication. This policy requires that all clinical trials be registered in a public trials registry. It will be the responsibility of IVAC/WHO to register this trial in an acceptable registry. ICMJE authorship criteria will be strictly followed for publication of any manuscript(s) arising from this trial. In addition, this trial, since funded by WHO, will follow the WHO Open Access Policy, which makes research funded by WHO and published in journals available to the public without a subscription necessary.

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APPENDIX A

WHO Summary Table of Whole Virion A/H5N1 Influenza Vaccination Schedule by Manufacturer

(*Source:* www.who.int/entity/immunization/research/development/flu_trials_tables/en/**)**

Producer	Adjuvant	Dose	Schedule	% Responders at a Specified Titer	Seroconversion Rate	GMT Increase
Baxter (Czech Republic/ Austria)	Al(OH)3	3.75, 7.5, 15, 30, 45	Two doses at day 0, 21	NT≥20 after two doses: 66% (30µg+Alum) 61% (15µg+Alum) 64% (7.5µg+Alum) 69% (3.75µg+Alum) 71% (15µg no Alum) 76% (7.5µg no Alum)	NT≥4 fold increase after 2 doses: 51% (7.5µg+Alum) 55% (3.75µg+Alum) 69% (7.5µg no Alum)	Fold increase in NT after 2 doses: 4.6 (30µg+Alum) 3.9 (15µg+Alum) 4.0 (7.5µg+Alum) 4.4 (3.75µg+Alum) 5.7 (15µg no Alum) 5.3 (7.5µg no Alum)
Baxter (Czech Republic/ Austria)	Al(OH)3; None	7.5, 15, 45	Two doses	NI≥40 after 2 doses: 40% (45µg no Alum) 12% (15µg+Alum) 20% (15µg no Alum) 8% (7.5µg+Alum) 19% (7.5µg no Alum)	NI≥4 old increase after 2 doses: 40% (45µg no Alum) 12% (15µg+Alum) 18% (15µg no Alum) 8% (7.5µg+Alum) 19% (7.5µg no Alum)	No data
Baxter (Czech Republic/ Austria)	Al(OH)3	3.75, 7.5, 15, 30 - priming; 7.5 - booster	Priming: two doses; Booster: one dose 12-17 months after priming	NT≥20 after boost against strains: 97% A/Indonesia 96% A/vietnam 96% A/turkey/Turkey 83% A/Anhui	No data	No data
Biken, Japan	Al(OH)3	1.7, 5, 15	Two doses at day 0, 21	NT≥40 after 2 doses: IM SC 95% 84% (15µg+Alum) 70% 80% (5µg+Alum) 60% 53% (1.7µg+Alum)	NT≥4 fold increase after 2 doses: IM SC 95% 79% (15µg+Alum) 65% 75% (5µg+Alum) 40% 47% (1.7µg+Alum)	Fold Increase in NT after 2 doses: IM SC 14.0 13.3 (15µg+Alum) 7.0 5.7 (5µg+Alum) 2.9 3.4 (1.7µg+Alum)
Biken, Japan	Al(OH)3	5, 15	Two doses at day 0, 21	NT≥40 after 2 doses = 85% (15µg+Alum) 57% (5µg+Alum)	NT≥ 4 fold increase in NT after 2 doses: 71% (15µg+Alum) 45% (5µg+Alum)	Fold increase in NT after 2 doses: 4.7 (15µg+Alum) 2.6 (5µg+Alum)
Denka Seiken, Japan	Al(OH)3	1.7, 5, 15	Two doses at day 0, 21	No data	No data	No data
Denka Seiken, Japan	Al(OH)3	5, 15	Two doses at day 0, 21	No data	No data	No data

Producer	Adjuvant	Dose	Schedule	% Responders at a Specified Titer	Seroconversion Rate	GMT Increase
Kitasato Institute, Japan	Al(OH)3	1.7, 5, 15	Two doses at day 0, 21	No data	NT≥4 fold increase after 2 doses: IM SC 100% 74% (15µg+Alum) 75% 58% (5µg+Alum) 50% 25% (1.7µg+Alum)	Fold Increase in NT after 2 doses: SC 41.5 (15µg+Alum) 29.9 (5µg+Alum) 12.7 (5µg+Alum)
Kitasato Institute, Japan	Al(OH)3	5, 15	Two doses at day 0, 21	No data	NT≥ 4 fold increase after 2 doses: 81% (15µg+Alum) 65% (5µg+Alum)	Fold increase in NT after 2 doses: 5.1 (15µg+Alum) 3.7 (5µg+Alum)
Kaketsuken, Japan	Al(OH)3	1.7, 5, 15	Two doses at day 0, 21	NT≥40 after 2 doses: IM SC 45% 37% (15µg+Alum) 20% 5% (5µg+Alum)	NT≥4 fold increase after 2 doses: IM SC 75% 68% (15µg+Alum) 50% 20% (5µg+Alum)	Fold increase in NT after 2 doses: IM SC 6.3 4.8 (15µg+Alum) 2.9 1.6 (5µg+Alum)
Kaketsuken, Japan	Al(OH)3	5, 15	Two doses at day 0, 21	NT≥40 after 2 doses: 77% (15µg+Alum) 53% (5µg+Alum)	NT≥ 4 fold increase after 2 doses: 86% (15µg+Alum) 56% (5µg+Alum)	Fold increase in NT after 2 doses: 8.9 (15µg+Alum) 4.3 (5µg+Alum)
Biken and Kitazato Institute, Japan	Al(OH)3	15	Two doses at day 0, 21	NT≥40 after 2 doses with Indonesia against: Indonesia Vietnam 74% 15%	NT≥4 fold increase after 2 doses with Anhui Ag against: Anhui Vietnam 82% 74%	Fold increase in NT after 2 doses with Indonesia against: Indonesia Vietnam 9.4 2.0
Biken and Kitazato Institute, Japan	Al(OH)3	15	Priming: two doses with Vietnam strain; Booster: single dose two years after priming	NT≥40 after boosting with Indonesia against: Indonesia Vietnam 92% 97%	NT≥4 fold increase after boosting with Anhui Ag: against: Anhui Vietnam 94% 1%	Fold increase in NT after boosting with Indonesia: against: Indonesia Vietnam 36.7 23.1
Biken and Kitazato Institute, Japan	Al(OH)3	15	Two doses at day 0, 21	No data	No data	No data

Producer	Adjuvant	Dose	Schedule	% Responders at a Specified Titer	Seroconversion Rate	GMT Increase
GSK Biologicals, Belgium	AlPO4; Al(OH)3	3.8, 7.5, 15, 27	Two doses at day 0, 21	HI≥40 after 2 doses: 90% (27mg+Alum) 71% (15mg+Alum) 63% (7.5mg+Alum) 69% (3.8mg+Alum) 71% (27mg non Alum) 70% (15mg non Alum) 58% (7.5mg non Alum) 51% (3.8mg non Alum)	HI≥4 fold increase after 2 doses: 90% (27mg+Alum) 71% (15mg+Alum) 63% (7.5mg+Alum) 67% (3.8mg+Alum) 71% (27mg no Alum) 0% (15mg no Alum) 58% (7.5mg no Alum) 51% (3.8mg+ no Alum)	Fold increase in HI after 2 doses: 32.4 (27mg+Alum) 12.4 (15mg+Alum) 9.1 (7.5mg+Alum) 10.5 (3.8mg+Alum) 13.0 (27mg non Alum) 10.9 (15mg non Alum) 7.9 (7.5mg non Alum) 5.7 (3.8mg non Alum)
Omninvest, Hungary	AlPO4	6	Single dose	HI≥40 = 63.7%	HI≥4 fold increase = 63.7%	HI fold increase in HI = 5.6
Omninvest, Hungary	AlPO4	6	Single dose	HI≥40: Adults Elderly 79% 61%	HI≥4 fold increase: Adults Elderly 91% 68%	HI fold increase: Adults Elderly 18.7 10.9
Omninvest, Hungary	AlPO4	6	Single dose	HI≥40: 75%	HI≥40: 75%	Fold increase in HI: 16.9
Omninvest, Hungary	AlPO4	3.5, 6, 12	Single or two doses	HI≥64 (adults) = 71% (12µg+Alum, 1 dose) 72% (6µg+Alum, 1 dose) 38% (3.5µg+Alum, 1 dose) 72% (3.5µg+Alum, 2 doses) HI≥64 (elderly) = 67% (12µg+Alum, 1 dose) 65% (6µg+Alum, 1 dose) 35% (3.5µg+Alum, 1 dose) 61% (3.5µg+Alum, 2 doses)	HI≥4 fold increase (adults) = 71% (12µg+Alum, 1 dose) 72% (6µg+Alum, 1 dose) 38% (3.5µg+Alum, 1 dose) 72% (3.5µg+Alum, 2 doses) HT≥4 fold increase (elderly) = 67% (12µg+Alum, 1 dose) 65% (6µg+Alum, 1 dose) 35% (3.5µg+Alum, 1 dose) 61% (3.5µg+Alum, 2 doses)	Fold increase in HI (adults) = 22.8 (12µg+Alum, 1 dose) 21.1 (6µg+Alum, 1 dose) 11.1 (3.5µg+Alum, 1 dose) 19.9 (3.5µg+Alum, 2 doses) Fold increase in HI (elderly) = 15.2 (12µg+Alum, 1 dose) 14.8 (6µg+Alum, 1 dose) 10.1 (3.5µg+Alum, 1 dose) 14.5 (3.5µg+Alum, 2 doses)

Producer	Adjuvant	Dose	Schedule	% Responders at a Specified Titer	Seroconversion Rate	GMT Increase
Sinovac Biotech, China	Al(OH)3	1.25, 2.5, 5, 10	Priming: two doses at day 0, 28; Booster: one dose	HI≥40 after: priming boosting 78% 90% (10µg+Alum) 33% 79% (5µg+Alum) 29% 31% (2.5µg+Alum) 13% 29% (1.25µg+Alum)	HI≥4 fold increase after: priming boosting 78% 80% (10µg+Alum) 33% 79% (5µg+Alum) 24% 19% (2.5µg+Alum) 13% 24% (1.25µg+Alum)	Fold increase in HI after priming: 11.5 (10µg+Alum) 4.9 (5µg+Alum) 2.7 (2.5µg+Alum) 2.7 (1.25µg+alum)
Sinovac Biotech, China	Al(OH)3	5, 10, 15	Two doses at day 0, 14 or 0, 28	HI≥40 after 2 doses: 90% (15µg+Alum) 78% (10µg+Alum) 54% (5µg+Alum) NT≥40 after 2 doses: 100% (15µg+Alum) 96% (10µg+Alum) 94% (5µg+Alum)	HI≥4 fold increase after 2 doses: 90% (15µg+Alum) 78% (10µg+Alum) 53% (5µg+Alum) HT≥4 fold increase after 2 doses: 100% (15µg+Alum) 92% (10µg+Alum) 91% (5µg+Alum)	Fold increase in HI after 2 doses: 18.2 (15µg+Alum) 12.4 (10µg+Alum) 6.3 (5µg+Alum) Fold increase in NT after 2 doses: 30.4 (15µg+Alum) 21.9 (10µg+Alum) 13.5 (5µg+Alum)
Sinovac Biotech, China	Al(OH)3	5	Two doses at day 0, 28	HI≥40 after two doses: 45%	HI≥4 fold increase after 2 doses: 45%	Fold increase in HI after two doses: 6.0
Sinovac Biotech, China	Al(OH)3	10	Two doses at day 0, 28	HI≥40 : 49%	HI≥4 fold increase after 2 doses: 48%	Fold increase in HI: 5.5
Sinovac Biotech, China	Al(OH)3	1.25, 2.5, 5, 10	Priming: two doses; Booster: one dose 12 months after priming	≥40 after 3 doses: HI NT 90% 100% (10µg+Alum) 79% 93% (5µg+Alum) 31% 81% (2,5µg+Alum) 29% 53% (1.25µg+Alum)	≥4 fold increase after 3 doses: HI NT 80% 90% (10µg+Alum) 79% 79% (5µg+Alum) 12% 62% (2.5µg+Alum) 24% 47% (1.25µg+Alum)	No data
Vabiotech, Vietnam	Al(OH)3	30	Two doses at day 0, 28	HI≥40 after 2 doses: 95.8% (30µg+Alum)	HI≥4 fold increase after 2 doses: 95.8% (15µg+Alum)	Fold increase in HI after 2 doses: 9.1 (30µg+Alum)

Producer	Adjuvant	Dose	Schedule	% Responders at a Specified Titer	Seroconversion Rate	GMT Increase
Vabiotech, Vietnam	Al(OH)3	3.75, 7.5, 15, 30, 45	Two doses at day 0, 28	HI≥40 after doses: 1 2 46% 97% (45µg) 42% 94% (30µg) 29% 83% (15µg) 26% 76% (7.5µg) 21% 61% (3.75µg)	HI≥4 fold increase after doses: 1 2 46% 97% (45µg) 42% 94% (30µg) 29% 83% (15µg) 26% 76% (7.5µg) 21% 61% (3.75µg)	Fold increase in HI after doses: 1 2 2.9 14.2 (45µg) 2.7 10.1 (30µg) 1.6 6.1 (15µg) 1.8 3.9 (7.5µg) 1.6 3.1 (3.75%)
Vabiotech, Vietnam	Al(OH)3	30	Two doses at day 0, 28	HI≥40 after 2 doses: 92% with strain 30408, Clade 1 79% with strain 31244, Clade 2	HI≥4 fold increase after 2 doses: 93% with strain 30408, Clade 1 81% with strain 31244, Clade 2	Fold increase after 2 doses: 8.1 with strain 30408, Clade 1 5.3 with strain31244, Clade 2
RIBSP, Kazakhstan	AL(OH)3	7.5, 15	Two doses at day 0, 21	HI≥40 after 1 and 2 doses: 1 2 67% 89% (15µg+ Alum) 17% 67% (7.5µg+Alum)	HI≥4 fold increase after 1 and 2 doses: 1 2 91% 89% (15µg+ Alum) 67% 75% (7.5µg+Alum)	Fold increase in HI after 1 and 2 doses: 1 2 8.0 10.6 (15µg+ Alum) 3.3 5.7 (7.5µg+Alum)
RIBSP, Kazakhstan	AL(OH)3	7.5, 15	Single dose	HI≥40 after 1 dose: 58% (15µg+ Alum) 53% (7.5µg+Alum)	HI≥4 fold increase after 1 dose: 70% (15µg+ Alum) 55% (7.5µg+Alum)	Fold increase in HI after 1 dose: 4.7 (15µg+ Alum) 3.5 (7.5µg+Alum)
Netherlands Vaccine Institute	None	15	Two doses at day 0, 21	HI ≥40 after 2 doses: 69%	HI≥4 fold increase after 2 doses: 69%	Fold increase in HI after 2 doses: 8.9

APPENDIX B

IVACFLU-A/H5N1
TABLE OF GRADING SEVERITY FOR CERTAIN EVENTS[1]

I. Instructions and Clarifications

Estimating Severity Grade for Parameters Not Identified in the Table

In order to grade a clinical AE that is not identified in the DAIDS AE grading table, refer to the protocol.

Determining Severity Grade for Parameters "Between Grades"

If the severity of a clinical AE could fall under either one of two grades (e.g., the severity of an AE could be either Grade 2 or Grade 3), select the higher of the two grades for the AE. If a laboratory value that is graded as a multiple of the ULN or LLN falls between two grades, select the higher of the two grades for the AE. For example, Grade 1 is 2.5 x ULN and Grade 2 is 2.6 x ULN for a parameter. If the lab value is 2.53 x ULN (which is between the two grades), the severity of this AE would be Grade 2, the higher of the two grades.

Values Below Grade 1

Any laboratory value that is between either the LLN or ULN and Grade 1 should not be graded.

Determining Severity Grade when Local Laboratory Normal Values Overlap with Grade 1 Ranges

In these situations, the severity grading is based on the ranges in the DAIDS AE Grading Table, even when there is a reference to the local lab LLN.

For example: Phosphate, Serum, Low, Adult and Pediatric > 14 years Grade 1 range is 2.50 mg/dL - < LLN. A particular laboratory's normal range for Phosphate is 2.1 – 3.8 mg/dL. A participant's actual lab value is 2.5. In this case, the value of 2.5 exceeds the LLN for the local lab, but will be graded as Grade 1 per DAIDS AE Grading Table.

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[1] Based On The DAIDS Table For Grading the Severity of Adult And Pediatric Adverse Events, Version 2.0, November 2014; and Guidance For Industry: Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials; FDA, 2007.

II. Definitions of Terms Used in the Table:

Basic Self-care	Functions Adult Activities such as bathing, dressing, toileting, transfer/movement, continence, and feeding.
LLN	Lower limit of normal
Medical Intervention	Use of pharmacologic or biologic agent(s) for treatment of an AE
NA	Not Applicable
Operative Intervention	Surgical OR other invasive mechanical procedures.
ULN	Upper limit of normal
Usual Social & Functional Activities	Adult Adaptive tasks and desirable activities, such as going to work, shopping, cooking, use of transportation, pursuing a hobby, etc.

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
ESTIMATING SEVERITY GRADE				
SYSTEMIC				
Acute Allergic Reaction	Localized urticaria (wheals) with no medical intervention indicated	Localized urticaria with intervention indicated OR Mild angioedema with no intervention indicated	Generalized urticaria OR Angioedema with intervention indicated OR Symptoms of mild bronchospasm	Acute anaphylaxis OR Life-threatening bronchospasm OR Laryngeal edema
Chills	Symptoms causing no or minimal interference with usual social & functional activities	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	NA
Fatigue or Malaise *Report only one*	Symptoms causing no or minimal interference with usual social & functional activities	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	Incapacitating symptoms of fatigue or malaise causing inability to perform basic self-care functions
Arthralgia (Joint Pain)	Joint pain causing no or minimal interference with usual social & functional activities	Joint pain causing greater than minimal interference with usual social & functional activities	Joint pain causing inability to perform usual social & functional activities	Incapacitating joint pain causing inability to perform basic self-care functions
Fever (non-axillary temperatures only)	38.0 to < 38.6°C	≥ 38.6 to < 39.3°C	≥ 39.3 to < 40.0°C	≥ 40.0°C
Fever (axillary)	37.7 – 38.1°C	38.2 – 38.8°C	38.9 – 40.0°C	> 40.0°C
Nausea	Transient (< 24 hours) or intermittent AND No or minimal interference with oral intake	Persistent nausea resulting in decreased oral intake for 24 to 48 hours	Persistent nausea resulting in minimal oral intake for > 48 hours OR Rehydration indicated (e.g., IV fluids)	Life-threatening consequences (e.g., hypotensive shock)
Vomiting	Transient or intermittent AND No or minimal interference with oral intake	Frequent episodes with no or mild dehydration	Persistent vomiting resulting in orthostatic hypotension OR Aggressive rehydration indicated (e.g., IV fluids)	Life-threatening consequences (e.g., hypotensive shock
Headache	Symptoms causing no or minimal interference with usual social & functional activities	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	Symptoms causing inability to perform basic self-care functions OR Hospitalization indicated OR Headache with significant impairment of alertness or other neurologic function

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
INJECTION SITE REACTIONS				
Injection Site Pain or Tenderness *Report only one*	Pain or tenderness causing no or minimal limitation of use of limb	Pain or tenderness causing greater than minimal limitation of use of limb	Pain or tenderness causing inability to perform usual social & functional activities	Pain or tenderness causing inability to perform basic self-care function OR Hospitalization indicated
Injection Site Erythema or Redness *Report only one* *> 15 years of age*	2.5 to < 5 cm in diameter OR 6.25 to < 25 cm^2 surface area AND Symptoms causing no or minimal interference with usual social & functional activities	≥ 5 to < 10 cm in diameter OR ≥ 25 to < 100 cm^2 surface area OR Symptoms causing greater than minimal interference with usual social & functional activities	≥ 10 cm in diameter OR ≥ 100 cm^2 surface area OR Ulceration OR Secondary infection OR Phlebitis OR Sterile abscess OR Drainage OR Symptoms causing inability to perform usual social & functional activities	Potentially life-threatening consequences (e.g., abscess, exfoliative dermatitis, necrosis involving dermis or deeper tissue)
Injection Site Induration or Swelling *Report only one* *> 15 years of age*	Same as for **Injection Site Erythema or Redness,** *> 15 years of age*	Same as for **Injection Site Erythema or Redness,** *> 15 years of age*	Same as for **Injection Site Erythema or Redness,** *> 15 years of age*	Same as for **Injection Site Erythema or Redness,** *> 15 years of age*

LABORATORY				
PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
HEMATOLOGY *Standard International Units are listed in italics*				
Hemoglobin (Hgb)				
Comment: The conversion factor used to convert g/dL to mmol/L is 0.6206 and is the most commonly used conversion factor. For grading hemoglobin results obtained by an analytic method with a conversion factor other than 0.6206, the result must be converted to g/dL using the appropriate conversion factor for the particular laboratory.				
Hemoglobin, Low (g/dL; *mmol/L*) *≥ 13 years of age (male only)*	10.0 to 10.9 *6.19 to 6.76*	9.0 to < 10.0 *5.57 to < 6.19*	7.0 to < 9.0 *4.34 to < 5.57*	< 7.0 *< 4.34*
≥ 13 years of age (female only)	9.5 to 10.4 *5.88 to 6.48*	8.5 to < 9.5 *5.25 to < 5.88*	6.5 to < 8.5 *4.03 to < 5.25*	< 6.5 *< 4.03*
Platelets, Decreased (cells/mm^3; *cells/L*)	100,000 to < 124,999 *100.000 x 10^9 to < 124.999 x 10^9*	50,000 to < 100,000 *50.000 x 10^9 to < 100.000 x 10^9*	25,000 to < 50,000 *25.000 x 10^9 to < 50.000 x 10^9*	< 25,000 < *25.000 x 10^9*
WBC, Decreased (cells/mm^3; *cells/L*) *> 7 days of age*	2,000 to 2,499 *2.000 x 10^9 to 2.499 x 10^9*	1,500 to 1,999 *1.500 x 10^9 to 1.999 x 10^9*	1,000 to 1,499 *1.000 x 10^9 to 1.499 x 10^9*	< 1,000 *< 1.000 x 10^9*

LABORATORY				
PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
	CHEMISTRIES	*Standard International Units are listed in italics*		
ALT or SGPT, High *Report only one*	1.25 to < 2.5 x ULN	2.5 to < 5.0 x ULN	5.0 to < 10.0 x ULN	≥ 10.0 x ULN
Total Bilirubin, High *> 28 days of age*	1.1 to < 1.6 x ULN	1.6 to < 2.6 x ULN	2.6 to < 5.0 x ULN	≥ 5.0 x ULN
Creatinine, High	1.1 to 1.3 x ULN	> 1.3 to 1.8 x ULN OR Increase of > 0.3 mg/dL above baseline	> 1.8 to < 3.5 x ULN OR Increase of 1.5 to < 2.0 x above baseline	≥ 3.5 x ULN OR Increase of ≥ 2.0 x above baseline
Total Protein (FDA Table)	5.5 – 6.0	5.0 – 5.4	< 5.0	--

APPENDIX C

Quality Control Testing

NATIONAL INSTITUTE FOR CONTROL OF VACCINE AND BIOLOGICALS, MOH, VIETNAM
Dai Kim, Hoang Mai, Hanoi, Vietnam

QUALITY CONTROL RESULTS

Number: 00515/VXVR-DK
(Valid for registration)

Trademark: IVACFLU-A/H5N1 **Product name:** Influenza vaccine A/H5N1	**NICVB code:** 01215/QM-DK
Lot number (in vial label**):** 010215	**Lot number (**in box label**):** 010215
Manufacture date: 06 February 2015	**Expired date:** 24 February 2017
Packaging: 0.5ml/dose/vial	
Manufacturer: Institute of Vaccine and Medical Biologicals (IVAC)	**Samples from:** Institute of Vaccine and Medical Biologicals (IVAC)

This is to certify that:

A/H5N1 influenza vaccine (IVACFLU–A/H5N1) lot number 010215 (in the label) that were produced by the Institute of Vaccine and Medical Biologicals (IVAC) meets the requirements on physical properties, pH, Aluminum concentration, protein concentration, general safety, HA content, endotoxin, identity, sterility and review document according to standards of manufacturer.

Hanoi, 19 May, 2015
Vice Director of NICVB
(signed and sealed)

Doan Huu Thien

RESULTS:

#	Indicator/Testing	Acceptance criteria of the manufacturer	Method	NICVB results	
				Result	Evaluation
	Sterility	No growth of bacteria and fungi in culture medium after 14 days	SOP: MT01-01	Batch record	Pass
	Visual	The upper is opaque white, milky white in the bottom. After mixing become homogeneous solution, no sediment, no particle.	SOP: HL 01-14	Pass	Pass
	Filling volume (ml/vial)	≥ volume in label	SOP: HL 01-14	Pass	Pass
	pH	6.5 – 7.5	SOP: HL 01-09	7.22	Pass
	Protein content (□g/dose)	≤ 300 µg/vial	SOP: HL 01-10	99.12	Pass
	Aluminum content (mg/vial)	≤ 1.25 mg/vial	SOP: HL 01-11	0.21	Pass
	General safety	All the mice and guinea pigs are in good health and gain weight after 7 monitoring days	SOP: KĐQG21	Pass	Pass
	HA content	≥ 80% HA value in label	SOP: VR07-03	19.6 µg HA/vial	Pass
	HA Identity	Positive	SOP: VR07-03	Positive	Pass
	Endotoxin	≤ 100 EU/dose	SOP: VR01-45	5	Pass

Hanoi, 19 May, 2015
Vice Director of NICVB
(signed)

Doan Huu Thien

NATIONAL INSTITUTE FOR CONTROL OF VACCINE AND BIOLOGICALS, MOH, VIETNAM
Dai Kim, Hoang Mai, Hanoi, Vietnam

QUALITY CONTROL RESULTS

Number: 00915/VXVR-DK
(Valid for registration)

Trademark: IVACFLU-A/H5N1 **Product name:** Influenza vaccine A/H5N1	**NICVB code:** 01515/QM-DK
Lot number (in vial label**):** 040215	**Lot number (**in box label**):** 040215
Manufacture date: 09 February 2015	**Expired date:** 24 February 2017
Packaging: 0.5ml/dose/vial	
Manufacturer: Institute of Vaccine and Medical Biologicals (IVAC)	**Samples from:** Institute of Vaccine and Medical Biologicals (IVAC)

This is to certify that:

A/H5N1 influenza vaccine (IVACFLU–A/H5N1) lot number 040215 (in the label) that were produced by the Institute of Vaccine and Medical Biologicals (IVAC) meets the requirements on physical properties, pH, Aluminum concentration, protein concentration, general safety, HA content, endotoxin, identity, sterility and review document according to standards of manufacturer.

Hanoi, 21 May, 2015
Vice director of NICVB
(singed and sealed)

Doan Huu Thien

RESULTS:

#	Indicator/Testing	Acceptance criteria of the manufacturer	Method	NICVB results	
				Result	Evaluation
	Sterility	No growth of bacteria and fungi in culture medium after 14 days	SOP: MT01-01	Batch record	Pass
	Visual	The upper is opaque white, milky white in the bottom. After mixing become homogeneous solution, no sediment, no particle.	SOP: HL 01-14	Pass	Pass
	Filling volume (ml/vial)	≥ volume in label	SOP: HL 01-14	Pass	Pass
	pH	6.5 – 7.5	SOP: HL 01-09	7.11	Pass
	Protein content (□g/dose)	≤ 300 µg/vial	SOP: HL 01-10	96.04	Pass
	Aluminum content (mg/vial)	≤ 1.25 mg/vial	SOP: HL 01-11	0.21	Pass
	General safety	All the mice and guinea pigs are in good health and gain weight after 7 monitoring days	SOP: KĐQG21	Pass	Pass
	HA content	≥ 80% HA value in label	SOP: VR07-03	34.05 µg HA/vial	Pass
	HA Identity	Positive	SOP: VR07-03	Positive	Pass
	Endotoxin	≤ 100 EU/dose	SOP: VR01-45	5	Pass

Hanoi, 21 May, 2015
Vice Director of NICVB
(signed)

Doan Huu Thien

NATIONAL INSTITUTE FOR CONTROL OF VACCINE AND BIOLOGICALS, MOH, VIETNAM
Dai Kim, Hoang Mai, Hanoi, Vietnam

QUALITY CONTROL RESULTS

Number: 00715/VXVR-DK
(Valid for registration)

Trademark: PLACEBO **Product name:** PBS pH 7.2	**NICVB code:** 01815/QM-DK
Lot number (in vial label**):** 07P0215	**Lot number (**in box label**):** 07P0215
Manufacture date: 05 February 2015	**Expired date:** 24 February 2017
Packaging: 0.5ml/dose/vial	
Manufacturer: Institute of Vaccine and Medical Biologicals (IVAC)	**Samples from:** Institute of Vaccine and Medical Biologicals (IVAC)

This is to certify that:

PBS pH 7.2 (PLACEBO) lot number 07P0215 (in the label) that were produced by the Institute of Vaccine and Medical Biologicals (IVAC) meets the requirements on visual, physical properties, pH, NaCl concentration, general safety, endotoxin, sterility and review document according to standards of manufacturer.

Hanoi, 19 May, 2015
Vice director of NICVB
(singed and sealed)

Doan Huu Thien

RESULTS:

#	Indicator/Testing	Acceptance criteria of the manufacturer	Method	NICVB results	
				Result	Evaluation
	Sterility	No growth of bacteria and fungi in culture medium after 14 days	SOP: MT01-01	Batch record	Pass
	Visual	Clear solution, colorless, no sediment, and no particle.	SOP: HL 01-14	Pass	Pass
	Filling volume (ml/vial)	≥ 0.5 ml/vial	SOP: HL 01-14	Pass	Pass
	pH	6.5 – 7.5	SOP: HL 01-09	7.11	Pass
	NaCl content (%)	≤ 1%	SOP: HL 01-07	0.97%	Pass
	General safety	All the mice and guinea pigs are in good health and gain weight after 7 monitoring days	SOP: KĐQG21	Pass	Pass
	Endotoxin	≤ 1.25 EU/dose	SOP: VR01-45	0.078	Pass
	Endotoxin	≤ 100 EU/dose	SOP: VR01-45	5	Pass

Hanoi, 19 May, 2015
Vice Director of NICVB
(signed)

Doan Huu Thien

APPENDIX D

	ACTIVITY	(Investigator, Clinical Trial Unit, Clinical Site, Laboratories)	PATH	WHO	IVAC (Sponsor)	Data Management (CRO)
	Objective 1: Phase 2/3 Study Developed					
1	**Develop protocol**					
	Draft protocol synopsis prepared	C	R	C	C	
	Protocol drafted	C	R	C	C	
	Protocol finalized and ready for submission	A	R	C	A	
2	**Prepare investigational product and placebo**					
	Prepare summary batch record for production and QC testing for 3 lots	I	I	I	R	
	Send samples of 3 lots to NICVB for release testing	I	I	I	R	
	Conduct pre-clinical study	I	C	I	R	
	Filling, packaging, labelling investigational product and placebo	I	C	I	R	
	QC testing for placebo	I	I	I	R	
	Coding investigational product and placebo	I	R	I	R	
3	**Select CTU and site**					
	Clinical site(s) initially assessed/proposed	C	R	I	C	
	Clinical site agreed upon	R		I	A	
	Specialty (serology) lab(s) initially assessed/proposed	C	R	I	C	
	Specialty (serology) lab(s) agreed upon	R	R	I	C	
	Externally validate specialty (serology) lab(s) profanely	C	R	I	C	
4	**Register Phase 2/3 study**					

	ACTIVITY	(Investigator, Clinical Trial Unit, Clinical Site, Laboratories)	PATH	WHO	IVAC (Sponsor)	Data Management (CRO)
	Petition to conduct clinical trial submitted (including proposed site, PI and Protocol Synopsis)	I	C	I	R	
	Investigator's Brochure completed for submission	I	C	I	R	
	- Summary information on investigational product prepared	I	C	I	R	
	-Summary information on MSV/WSV prepared	I	C	I	R	
	- Lot release certificates from NICVB for 3 consecutive lots obtained	I	C	I	R	
	-Report on pre-clinical studies prepared	I	C	I	R	
	Receives MOH approval or address MOH feedback on "registration"	I	C	I	R	
5	**Develop investigational dossier**					
	Investigator's Brochure provided to site	I	I	C	R	
	Informed consent forms (ICFs) finalized and translated	R	A	C	I	
	Clinical Trial Agreement (CTA) drafted	C	C	A	R	
	CTU/site budget preparation	R	A	C	I	
	Additional specialty lab budget preparation	R	A	C	I	
	CTU/site and additional specialty lab budgets and CTA language agreed (between CTU/site, additional lab, PATH, WHO and IVAC)	R	R	C	R	
	Contract for Clinical trial and MOU prepared and signed	R	A	A	R	
	Insurances for subjects, researchers	I	C	R	R	

	ACTIVITY	(Investigator, Clinical Trial Unit, Clinical Site, Laboratories)	PATH	WHO	IVAC (Sponsor)	Data Management (CRO)
	Clinical Trial Agreement signed by parties after MOH approval	R	I	A	R	
6	**"Investigational dossier" approved**					
	"Application" form submitted	R	C	I	C	
	"Description of the Proposal" form submitted	R	C	I	C	
	MOU submitted	R	C	I	C	
	"Informed Consent" form submitted	R	C	I	C	
	CV and GCP certificate of PI submitted	R	C	I	C	
	Meeting minutes of the IRB of Study site review meeting submitted	R	C	I	C	
	Support letter from provincial level (field site) submitted	R	C	I	C	
	Sample of label of investigational product (*product for clinical trial only, not permitted for other purpose*)	C	R	I	C	
	Present/Defend the dossier to MOH	R	C	I	C	
	Receives approval or feedback from MOH on investigational dossier	R	I	I	I	
	Addresses any issues raised by MOH	R	C	I	C	
	Objective 2: Phase 2/3 Study Implemented					
7	**Pre- trial preparation**					
	Other ethics submission(s) and correspondence (in addition to MOH)					
	PATH (WIRB)	I	R	I	I	
	WHO (ERC)	C	R	A	I	
	Local site/institutional IRBs	R	I	I	I	

	ACTIVITY	(Investigator, Clinical Trial Unit, Clinical Site, Laboratories)	PATH	WHO	IVAC (Sponsor)	Data Management (CRO)
	Local People's Committee approval and communication	R	I	I	I	
	Pre-study progress reporting	R	A	I	I	
	Randomization plan developed	I	R	I	C	
	Clinical monitoring plan developed	I	R	I	C	
	Safety monitoring plan developed	I	R	I	C	
	Study registered with international trial registry	I	R	C	I	
	Lab reagents/materials for taking blood purchased	R	I	A	I	
	Preparation meeting with field site staff and community	R	C	I	I	
	The list of eligible subjects constructed	R	C	I	I	
8	**Develop study materials**					
	Investigator's File established (including all logs)	R	C/A	I	I	
	Protocol issued to investigative staff	R	R	I	I	
	Site SOP's developed	R	R	I	I	
	CRFs and completion guidelines developed	C	R	I	I	
	SOPs relating to cold chain maintenance developed	R	R	I	A	
	ICFs and CRFs printed and transported to site	I	R	I	I	
9	**Pre-trial training**					
	Ethics training for required personnel provided	C	R	I	I	
	GCP training for required personnel provided	C	R	I	I	
	Protocol training for sub-investigators and staff provided	R	C/A	I	I	
	Trial practice run training conducted	R	C/A	I	I	
10	**Vaccine transportation and management**					

	ACTIVITY	(Investigator, Clinical Trial Unit, Clinical Site, Laboratories)	PATH	WHO	IVAC (Sponsor)	Data Management (CRO)
	Pre-trial cold-chain assessment	C	R	I	I	
	Provide Certificate of Analysis to site	I	I	I	R	
	Provide shipment information to site and/or handling agent	I	I	I	R	
	Shipment of vaccine to site	I	I	I	R	
	Receipt of vaccine at site	R	I	I	I	
	Return of unused vaccine to manufacturer	R	I	I	A	
11	**Overall study responsibilities fulfilled**					
	Investigative staff identified, recruited and/or hired	R	I	I	I	
	Financial management	R	I	C	I	
	Study teleconference organization	I	R	I	I	
	Study teleconference participation	R	R	I	R	
	Study implementation	R	C/A	I	C	
	Progress reports to WHO, PATH and IVAC	R	I	I	I	
12	**Conduct transport and testing of biological specimens**					
	Clinical Laboratory					
	Coordination of transport of samples from sites to clinical lab	R	I	I	I	
	Laboratory sample testing	R	A	I	I	
	Specialty Laboratory(s) (serology)					
	Coordination of transport of samples from site to specialty lab(s)	R	I	I	I	
	Laboratory sample testing	R	A	I	A	
13	**Clinical/Medical Monitoring**					
	Conduct/participate in pre-study site visits	R	R	I	I	

	ACTIVITY	(Investigator, Clinical Trial Unit, Clinical Site, Laboratories)	PATH	WHO	IVAC (Sponsor)	Data Management (CRO)
	Conduct/participate in site initiation	R	R	I		
	Conduct/participate in interim monitoring	R	R	I	I	
	Conduct/participate in close out	R	R	I	I	
	Prepare initiation/interim monitoring/close-out reports	I	R	I	I	
	Review CRFs and assure resolution of findings	C	R	I	I	
	Establish 24-hour coverage for SAEs	R	A	I	I	
	Write initial and follow-up SAE reports	R	I	I	I	
	Provide SAE medical review	I	R	I	C	
	Maintain SAE log	R	C	I	I	
	Prepare progress and compliance reports for WHO, PATH, IVAC and MOH	R	I	I	I	
14	**Assure Medical/Ethical Compliance:**					
	Maintain Investigator's File	R	C	I	I	
	Immediate SAE reporting to ERCs and MOH, per ICH and ERC guidelines	R	C	I	I	
	Safety reporting to MOH, if required	R	C	I	I	
	Submission of compliance reports to MOH, as required	C	C	I	R	
15	**Ensure QA/QC for study implementation**					
	Provide ongoing Quality Control for study implementation	R	I	I	I	
	Perform Quality Assurance / Site Audits	I	R	I	I	
	Flag recruitment and challenges affecting quality	R	I	I	I	
	Implement corrective actions	R	A	I	I	

	ACTIVITY	(Investigator, Clinical Trial Unit, Clinical Site, Laboratories)	PATH	WHO	IVAC (Sponsor)	Data Management (CRO)
	Provide ongoing Quality Control for Specialty Laboratory	R	I	I	I	
	Perform Quality Assurance for Specialty Laboratory	C	R	I	I	
	Coordination for MOH inspection of trial	R	I	I	R	
16	**Data Management**					
	CRO identified for data management	I	R	A	C	
	Data management plan developed	C	A	I	C	R
	Data entry guidelines developed (design, planning and data entry)	I	A	I	I	R
	Data entry conducted	I	I	I	I	R
	Data cleaning conducted	I	I	I	I	R
	Data queries resolved	R	C	I	I	R
	Data certified as accurate	I	A	I	I	R
	Database locked	I	A	I	I	R
	Documents and data archived	I	I	I	I	R
	Laboratory Results sent to Data Management	R	A	I	I	A
	Laboratory Results merged with clinical database	I	I	I	I	R
	Database transferred to (PATH or other) statistician	I	A	I	I	R
17	**Statistical Analysis**					
	Statistical analysis plan developed	C	R	I	A	
	Conduct analysis according to statistical analysis plan	I	R	I	I	
	Results report provided for review	I	R	A	I	
	Results report reviewed with comments to PATH	R	I	A	R	
	Clinical Study Report written	C	R	A	C	

	ACTIVITY	(Investigator, Clinical Trial Unit, Clinical Site, Laboratories)	PATH	WHO	IVAC (Sponsor)	Data Management (CRO)
	CSR reviewed and approved by partners	R	I	A	R	
	CSR submitted to MOH for approval	R	I	A	C	
	Manuscript of results drafted	C	R	A	C	
	Manuscript of results submitted for publication	A	R	A	A	
	R=party which is Responsible for carrying out the activity					
	A=party which Approves outcome					
	C=party which is Consulted and provides input to party R					
	I=party which is Informed of the outcome of the activity					