**ClinicalTrials.gov Protocol Registration and Results System (PRS) Receipt**
Release Date: March 5, 2019

**ClinicalTrials.gov ID: NCT03390166**

## Study Identification

| | |
|---|---|
| Unique Protocol ID: | Tri Fluvac Vaccine phase 2/3 |
| Brief Title: | Immunogenicity and Safety of Tri Fluvac, a Seasonal Trivalent Inactivated Influenza Vaccine in Healthy Thai Adults |
| Official Title: | A Phase II/III Double Blinded, Randomized, Controlled, Non-inferiority Trial to Evaluate the Immunogenicity and Safety of Tri Fluvac, a Seasonal Trivalent Inactivated Split Virion Influenza Vaccine, in Healthy Thai Subjects Aged 18-49 Years |
| Secondary IDs: | |

## Study Status

| | |
|---|---|
| Record Verification: | March 2019 |
| Overall Status: | Completed |
| Study Start: | July 24, 2017 [Actual] |
| Primary Completion: | March 31, 2018 [Actual] |
| Study Completion: | February 12, 2019 [Actual] |

## Sponsor/Collaborators

| | |
|---|---|
| Sponsor: | Mahidol University |
| Responsible Party: | Principal Investigator<br>Investigator: Punnee Pitisuttithum [ppitisuthitham]<br>Official Title: Prof.<br>Affiliation: Mahidol University |
| Collaborators: | The Government Pharmaceutical Organization<br>World Health Organization |

## Oversight

| | |
|---|---|
| U.S. FDA-regulated Drug: | No |
| U.S. FDA-regulated Device: | No |
| U.S. FDA IND/IDE: | No |
| Human Subjects Review: | Board Status: Approved<br>Approval Number: MUTM 2017-020-01<br>Board Name: Ethics Comittee of the Faculty of Tropical Medicine<br>Board Affiliation: Faculty of Tropical Medicine, Mahidol University<br>Phone: (662) 3069100 |

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Address:

Faculty of Tropical Medicine, Mahidol University
420/6 Rajvithi road, Ratchathewi, Bangkok 10400
Thailand

Data Monitoring: Yes

FDA Regulated Intervention: No

## Study Description

Brief Summary: The study is aim to evaluate the immunogenicity and safety with two groups of participants who will received a seasonal trivalent split, inactivated influenza vaccine (A/H1N1; A/H3N2 and B) or an active comparator (licensed influenza vaccine

Detailed Description: This is a phase II/III, non-inferiority double-blinded, randomized, controlled trial of immunogenicity and safety with two groups of participants who will received a seasonal trivalent split, inactivated influenza vaccine (A/H1N1; A/H3N2 and B) or an active comparator (licensed influenza vaccine).

A total of about 945 healthy Thai male and female adult volunteers 18 through 49 years of age; 630 participants will be randomized to receive the GPO Tri Fluvac and 315 will receive an active comparator (a 2:1 ratio) (inclusion of ~7% lost to follow-up).

Safety will be assessed for all participants through Day 90 after vaccination. Immunogenicity will be assessed in serum samples obtained at baseline and 21 days after vaccination in a subset of at least 586 individuals randomized to study vaccine and 293 active comparator vaccine recipients.

## Conditions

Conditions: Influenza

Keywords: GPO Tri Fluvac Vaccine
Tri Fluvac vaccine

## Study Design

Study Type: Interventional

Primary Purpose: Prevention

Study Phase: Phase 2/Phase 3

Interventional Study Model: Parallel Assignment
non-inferiority double-blinded, randomized, controlled trial

Number of Arms: 2

Masking: Double (Participant, Investigator)
double blinded

Allocation: Randomized

Enrollment: 945 [Actual]

## Arms and Interventions

| Arms | Assigned Interventions |
|---|---|
| Active Comparator: GPO Tri Fluvac vaccine<br>630 volunteers will receive a single dose of the seasonal trivalent inactivated influenza vaccine (consisting of A/Michigan/45/2015 (H1N1)pdm-09-like virus, A/Hong Kong/4801/2014 (H3N2)-like virus, and B/Brisbane/60/2008-like virus) produced by GPO Thailand. To be administered via the intramuscular route; the preferred injection site will be the deltoid of the non-dominant arm. | Biological/Vaccine: GPO Tri Fluvac vaccine<br>The vaccine will be administered via the intramuscular route; the preferred injection site will be the deltoid of the non-dominant arm. |
| Active Comparator: Licensed Influenza vaccine<br>315 volunteers will receive acLicensed Influenza vaccine (seasonal trivalent inactivated split virion influenza vaccine recommended for Southern Hemisphere in 2017 (consisting of A/Michigan/45/2015 (H1N1)pdm-09-like virus, A/Hong Kong/4801/2014 (H3N2)-like virus, and B/Brisbane/60/2008-like virus) 0.5 mL administered intramuscularly (IM) in the deltoid muscle of the non-dominant arm. | Biological/Vaccine: Licensed influenza vaccine<br>The comparator licensed influenza vaccine will be administered via the intramuscular route; the preferred injection site will be the deltoid of the non-dominant arm. |

## Outcome Measures

Primary Outcome Measure:

1. Primary Immunogenicity Endpoint: Immune responses to the GPO Tri Fluvac and active comparator vaccine at 21 days post-injection.
   null [Time Frame: 21 days post-injection]

2. Primary Safety Endpoints: Number of subjects with all Adverse Events during the study period and % of subjects with all Adverse Events during the study period
   null [Time Frame: upto 90 days]

## Eligibility

Minimum Age: 18 Years

Maximum Age: 49 Years

Sex: All

Gender Based:

Accepts Healthy Volunteers: Yes

Criteria: Inclusion Criteria:

- Age 18-49 years old on the day of screening, having Thai ID card or equivalent
- Able to read and write in Thai and sign written informed consent form
- Able to attend all scheduled visits and to comply with all trial procedures.
- Healthy or medically stable, as established by medical history and physical examination. For individuals with medical conditions, symptoms/signs, if present must be stable, under control or unchanged for the past three months. If medication is used to treat the condition, the medication dose must have been stable for at least one month preceding vaccination.
- For female participants:

- Not breast feeding, non-pregnant (based on negative urine pregnancy test) and no plan to become pregnant up to Day 60.
- Women who are not surgically sterile (hysterectomy or tubal ligation) or post-menopausal for more than one year must be willing to use effective contraceptive method to prevent pregnancy until Day 60 after vaccination. Effective methods include intrauterine device, hormonal contraceptives (oral, injectable, patch, implant, ring) or double barrier contraceptives (condom or diaphragm with spermicide). Women with credible history of abstinence may be enrolled at the discretion of the investigator

Exclusion Criteria:

- Participation in another clinical trial involving any therapy within the previous three months or planned enrollment in such a trial during the period of this study.
- Hypersensitivity after previous administration of any vaccine.
- Having a history of H1N1, H3N2 or Flu B infection within 3 months preceding enrollment to the trial
- Vaccination against influenza in the past 6 months preceding enrollment to the trial
- Receipt of any non-study vaccine within four weeks prior to enrollment or refusal to postpone receipt of such vaccines until after the Day 21 visit.
- History of bronchial asthma, chronic lung diseases, chronic rhinitis
- History of immunodeficiency state
- History of immunosuppression < 6 months prior to immunization
- History of anaphylactic or other allergic reactions to influenza vaccine or any vaccine component or excipient (e.g. gentamicin or thimerosal)
- History of Guillain-Barré Syndrome.
- Having acute infection with fever > 38 degree Celsius or noninfectious diseases (within 72 hours) preceding enrollment in the trial
- Volunteers who have been taking immunoglobulin products or have had a blood transfusion during past 3 months before the beginning of the trial or planned receipt of such products prior to the Day 21 visit.
- Current alcohol abuse or drug addiction that might interfere with the ability to comply with trial procedures
- Any condition that in the opinion of the investigator would pose a health risk to the subject if enrolled, or could interfere with the evaluation of the vaccine

## Contacts/Locations


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Locations: **Thailand**


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## IPDSharing

Plan to Share IPD: Undecided

## References

Citations:

Links:

Available IPD/Information:

U.S. National Library of Medicine | U.S. National Institutes of Health | U.S. Department of Health & Human Services

**Protocol No.:** GPO Tri Fluvac Vaccine Phase II/III

**TITLE:** A Phase II/III Double Blinded, Randomized, Controlled, Non-inferiority trial to evaluate the Immunogenicity and Safety of Tri Fluvac, a Seasonal Trivalent Inactivated split virion Influenza vaccine, in healthy THAI subjects aged 18 – 49 years.

**PARTICIPATING INSTITUTIONS**

**INVESTIGATORS:**

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Focal point: Erin Sparrow, +41 22 791 1238

Role of WHO: WHO will provide financial support for the trial and will be informed immediately of any SAE as specified in the protocol, which they may choose to forward to the WHO Ethics Review Committee if deemed appropriate.

**MANUFACTURER:**

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**INSTITUTIONAL REVIEW BOARD/ETHICS REVIEW COMMITTEE:**

WHO ERC (WHO Ethics Review Committee) and the Ethics Committee of the Faculty of Tropical Medicine, Mahidol University

**DURATION:** 12 months

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**STATEMENT OF COMPLIANCE**

I am Prof.Dr. Punnee Pitisuttithum, principal investigator of the study "A Phase II/III Double Blinded, Randomized, Controlled, Non-inferiority trial to evaluate the Immunogenicity and Safety of Tri Fluvac, a Seasonal Trivalent Inactivated split virion Influenza vaccine, in healthy Thai subjects aged 18 – 49 years". By signing below, I ensure that the study will be carried out on schedule, according to the content of the approved protocol, and in accordance with Good Clinical Practice (GCP) as required by applicable rules of Thailand and in accordance with the International Conference on Harmonization (ICH) E6: Good Clinical Practice: Consolidated Guideline.

The study informed consent documents will embody the elements of consent as described in the Declaration of Helsinki, 2013.

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.

This document contains confidential information not to be disclosed to anyone other than the Sponsor, the Investigator Team, and members of the Ethics Committee, unless authorized to do so by the Sponsor.

I declare that I have no potential or real conflict of interests.

Bangkok, Thailand

Principal Investigator

Confidentiality Statement:

The information contained in this document is provided for the exclusive use of investigators of this product and is subject to recall at any time. The information in this document may not be disclosed unless applicable laws or regulations require such disclosure. Subject to the foregoing, this information may be disclosed only to those persons involved in the study who have a need to know, with the obligation not to further disseminate this information.

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**LIST OF ABBREVIATIONS**

| | |
|---|---|
| AE | Adverse Event |
| CI | Confidence Interval |
| cm | Centimeter |
| CPMP | Committee for Proprietary Medicinal Products |
| CRF | Case Report Form |
| CRO | Contract Research Organization |
| CSR | Clinical Study Report |
| °C | Degrees Celsius |
| D | Day |
| EDC | Electronic Data Capture |
| EMA | European Medicine Agency |
| GCP | Good Clinical Practice |
| GMFR | Geometric Mean Fold Rises |
| GMT | Geometric Mean Titer |
| GPO | The Government Pharmaceutical Organization |
| HA | Hemagglutinin |
| HI | Hemagglutination Inhibition assay |
| hCG | Human Chorionic Gonadotropin |
| ICF | Informed Consent Form |
| ICH | International Conference on Harmonization |
| IEC | Independent Ethics Committee |
| IM | Intramuscular |
| IRB | Institutional Review Board |
| IWRS | Interactive Web Response System |
| LAIV | Live Attenuated Influenza Vaccine |
| LEC | Local Ethics Committee |
| LLN | Lower Limit of Normal |
| mcg | Microgram |
| mL | Milliliter |
| N | Number (typically refers to number of participants) |
| NIBSC-UK | National Institute for Biological Standards and Control–United Kingdom |
| NRA | National Regulatory Authorities |
| PI | Principal Investigator |

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PBS Phosphate buffered saline

SMT Safety Medical Team

SAE Serious Adverse Event

SAP Statistical Analysis Plan

SOP Standard Operating Procedure

TIV Trivalent Inactivated Influenza Vaccine

ULN Upper Limit of Normal

WHO World Health Organization

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## 1. PROTOCOL SUMMARY

| | |
|---|---|
| Title: | A Phase II/III Double Blinded, Randomized, Controlled, Non-inferiority trial to evaluate the Immunogenicity and Safety of Tri Fluvac, a Seasonal Trivalent Inactivated Split Virion Influenza Vaccine, in Healthy Thai Subjects Aged 18 – 49 Years. |
| Protocol #: | GPO Tri Fluvac Vaccine Phase II/III |
| Description of Study Design: | This is a phase II/III, non-inferiority double-blinded, randomized, controlled trial of immunogenicity and safety with two groups of participants who will received a seasonal trivalent split, inactivated influenza vaccine (A/H1N1; A/H3N2 and B) or an active comparator (licensed influenza vaccine).<br><br>A total of about 945 healthy Thai male and female adult volunteers 18 through 49 years of age; 630 participants will be randomized to receive the GPO Tri Fluvac and 315 will receive an active comparator (a 2:1 ratio) (inclusion of ~7% lost to follow-up).<br><br>Safety will be assessed for all participants through Day 90 after vaccination. Immunogenicity will be assessed in serum samples obtained at baseline and 21 days after vaccination in a subset of at least 586 individuals randomized to study vaccine and 293 active comparator vaccine recipients. |
| Study Hypothesis: | **Immunogenicity:** A single dose of the GPO seasonal trivalent split, inactivated influenza vaccine will induce immune responses measured by HI assay to each of the three vaccine antigens and will be non-inferior to active licensed comparator vaccine.<br><br>**Safety**: A single dose of the GPO seasonal trivalent split, inactivated influenza vaccine will be safe and well tolerated in adults 18 to 49 years of age. |
| Study Objectives: | **<u>Primary objective</u>**<br><br>**Immunogenicity**:<br><br>To evaluate the immunological non-inferiority seroconversion rate (using HI assay) and Geometric Mean Titre (GMT) of the GPO seasonal trivalent split, inactivated influenza vaccine compared to active comparator vaccine for each of the three vaccine antigens, three weeks after immunization (Day 21) and at the end of follow-up period (Day 90).<br><br>**Safety:**<br><br>To evaluate the safety profile of a single intramuscular dose of the GPO seasonal trivalent split, inactivated influenza vaccine in adults 18 to 49 years of age.<br><br>To compare the solicited symptoms, AE and SAE between subjects who will receive GPO trivalent split, inactivated influenza vaccine and those who will receive active comparator vaccine.<br><br>**<u>Secondary objective</u>**<br><br>To evaluate the HI responses at 3 weeks after immunization in participants with or without pre-existing HI antibody. |

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|---|---|
| Study Endpoints and Statistical Analysis: | **Primary Immunogenicity Endpoint:**<br>Immune responses to the GPO Tri Fluvac and active comparator vaccine at 21 days post-injection will be analyzed by the following:<br>- Number and percentage of participants with seroconversion against each of the three vaccine antigens. Seroconversion is defined as a serum HI antibody titer meeting the following four fold rising criteria:<br>- Pre-vaccination titer <1:10 and a post-vaccination titer measured on Day 21 of ≥1:40; or<br>- Pre-vaccination titer ≥1:10 and at least a four-fold increase in post-vaccination measured on Day 21.<br>- Geometric mean titers (GMTs) of serum HI antibodies pre- (Day 0) and post-vaccination (Day 21) for each of the three vaccine antigens.<br>Note that 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). If a titer is reported as greater or equal to the upper limit of the assay, it will be set to that limit.<br>The analyses will be performed on the Total Vaccinated cohort (ITT) and According to Protocol (ATP) cohort for immunogenicity. The primary immunogenicity analysis will be based on the ATP cohort.<br>- The Total Vaccinated cohort will include all subjects with a documented vaccine administration.<br>- The ATP cohort for immunogenicity will include all evaluable subjects (i.e. those meeting all eligibility criteria, complying with the procedures and intervals defined in the protocol, with no elimination criteria during the study) for whom data concerning immunogenicity outcome variables were available for antibodies against at least one study vaccine antigen component after vaccination.<br><br>**Primary Safety Endpoints:**<br>Number and percentage of subjects with solicited local and systemic reactions during the three days post-injection. In addition, all adverse events (AE) and serious adverse events (SAEs), and new onset of chronic diseases (NOCDs) will be collected for the entire study period. Specifically, the following safety parameters will be monitored and analyzed in terms of the number and proportion of participants reporting the following events will be assessed:<br>• Solicited local adverse events, including redness/erythema, swelling/induration, pain and limitation of arm movement within 30 minutes of vaccination and over the 3-day period post vaccination (Day 0-3).<br>• Solicited systemic adverse events, including fever, fatigue/malaise, muscle aches, joint aches, chills, nausea and headache within 30 minutes of vaccination and over the 3-day period post vaccination (Day 0-3).<br>• Unsolicited adverse events (AEs) occurring within 90 days post vaccination. |

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- Serious Adverse Events (SAE) occurring during the entire study period (Days 0-90).

Occurrences 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. Percentage of participants experiencing each reaction or event, or at least one reaction or event will be calculated along with two-sided exact 95% CIs. The percentage of participants with solicited AE and SAEs will be compared between vaccine and comparator groups and a two-sided p-value of 0.05 will be considered statistically significant.

Inferential analyses

GMT ratios (GMT active comparator vaccine/GMT GPO Tri Fluvac) and difference of seroconversion rate (with two-sided 95% CI) related to the comparisons of interest will be computed. Acceptance value of GMT ratios at ≤ 1.5 and/or difference of seroconversion rate at ≤ 10% for the upper bound of the 95% CI will be considered for non-inferiority.

**Secondary Immunogenicity Endpoints and analysis:**

The secondary immunogenicity endpoints will be analyzed by the following:

- Number and percentage of participants with a HI antibody titer ≥1:40 (seroprotective level) to each of the three vaccine antigens measured on Day 21 and Day 90.
- Number and percentage of participants who develop at least a four-fold increase in HI antibody titers to each of the vaccine antigen post-vaccination measured on Day 21 and Day 90 segregated by pre-vaccination HI antibody titers (<1:10 or ≥1:10).
- Geometric mean fold rises (GMFRs) of serum HI antibodies (post-vaccination/pre-vaccination) for each of the three vaccine antigens.
- GMTs of serum HI antibodies pre- (Day 0) and post-vaccination (Day 21 and Day 90) for each of the three vaccine antigens segregated by pre-vaccination HI antibody titers (<1:10 or ≥1:10).
- GMFRs of serum HI antibodies (post-vaccination/pre-vaccination) for each of the three vaccine antigens segregated by pre-vaccination HI antibody titers (<1:10 or ≥1:10).

Sample Size Calculation (1) :

The sample size calculation was planned for the ratio of 2:1. The SAS 9.4 statistical software, was used to calculate the sample size needed for the study under the assumption of a non-inferiority trial for binary outcome endpoint.

According to the recommendations for the co-primary endpoints, the sample size calculation was based on the following primary endpoints:

- The difference in seroconversion rate of active comparator vaccine and Seroconversion rate of GPO Tri Fluvac should not exceed 10 percentage

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points.

- The difference in natural log of mean antibody titer between active comparator vaccine and GPO Tri Fluvac should not exceed 0.405, which is equivalence to the margin for GMT ratio = 1.5.

The sample size calculation was calculated using parameters of three strains of influenza under the study, including H1, H3, and Flu B. The parameter estimates for seroconversion and Standard deviation of natural log of antibody titer were obtained from previous study, phase II study of GPO Tri Fluvac.

| Influenza strain | Titer Visit | Treatment Group | Sero-conversion | Mean of ln(titer) | |
|---|---|---|---|---|---|
| H1 | Day 21 | Vaccine | 0.88 | 5.9728 | |
| H3 | Day 21 | Vaccine | 0.535 | 5.36976 | |
| Flu B | Day 21 | Vaccine | 0.865 | 4.75286 | |

The sample size calculation for non-inferiority test for proportions was performed with the margin of 0.1, assuming different seroconversion rate of the three influenza strain, and expected difference in seroconversion of the two groups is 0.000 with one-sided test alpha level 0.025 and power 0.8. Finally the sample size was adjusted for 7% not included in the ATP cohort. The required sample size for the study is as follow. The largest sample size required is 945 for total: 630 for study vaccine group and 315 for comparator vaccine group.

***Two group test of equivalence in proportions (large unequal n's)***

| | H1 | H3 | Flu B |
|---|---|---|---|
| **Test significance level, $\alpha$ (one- sided)** | 0.025 | 0.025 | 0.025 |
| **Standard proportion, $\pi_S$** | 0.880 | 0.535 | 0.865 |
| **Equivalence limit difference, $\pi_T - \pi_S$, $\Delta_0$** | 0.100 | 0.100 | 0.100 |
| **Test expected proportion, $\pi_T$** | 0.880 | 0.535 | 0.865 |
| **Expected difference, $\pi_T - \pi_S$, $\Delta_1$** | 0.000 | 0.000 | 0.000 |
| **Power ( % )** | 80 | 80 | 81 |
| **$n_S$** | 125 | *293* | 134 |
| **$n_T$** | 250 | *586* | 276 |
| **Ratio: $n_T / n_S$** | 2.000 | 2.000 | 2.000 |
| **$N = n_S + n_T$** | 375 | 879 | 414 |
| ***Adjusted 7% not included in the ATP cohort*** | | | |
| **$n_S$** | 134 | ***315*** | 148 |
| **$n_T$** | 268 | ***630*** | 296 |
| **$N = n_S + n_T$** | 402 | ***945*** | 444 |

The sample size calculation for noninferiority test comparing two mean was performed according to the standard deviation of natural log scale of antibody titer of the 3 influenza strains with the margin of 0.405 (equivalence to ln of GMT ratio at 1.5), assuming expected difference in mean of natural log scale of antibody titer between the two groups is 0.000 with one-sided test alpha level 0.025 and power 0.8. Finally the sample size was adjusted for 7% not included in the ATP cohort.

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The required sample size for the study is as follow. The largest sample size required is 354 for total: 236 for study vaccine group and 118 for comparator vaccine group.

***Two group t-test of equivalence in means (unequal n's)***

| | H1 | H3 | Flu B |
|---|---|---|---|
| **Test significance level, $\alpha$ (one-sided)** | 0.025 | 0.025 | 0.025 |
| **Equivalence limit difference, $\Delta_0$** | 0.405 | 0.405 | 0.405 |
| **Expected difference, $\Delta_1$** | 0.000 | 0.000 | 0.000 |
| **$\Delta_0 - \Delta_1$** | 0.405 | 0.405 | 0.405 |
| **Common standard deviation, $\sigma$** | 1.082 | 1.119 | 1.233 |
| **Power ( % )** | 80 | 80 | 80 |
| **n1** | 85 | 91 | 110 |
| **n2** | 170 | 182 | 220 |
| **Ratio: $n_2 / n_1$** | 2.000 | 2.000 | 2.000 |
| **$N = n_1 + n_2$** | 255 | 273 | 330 |
| ***Adjusted 7% not included in the ATP cohort*** | | | |
| **$n_S$** | 91 | 98 | **118** |
| **$n_T$** | 182 | 195 | **236** |
| **$N = n_S + n_T$** | 273 | 293 | **354** |

**Final sample sizes for the study after adjusted for 7% not included in the ATP cohort = *630:315***

| | |
|---|---|
| Study Population: | About 945 male and non-pregnant female adults, 18 to 49 years of age. |
| Eligibility Criteria: | Inclusion:<br>- Age 18-49 years old on the day of screening, having Thai ID card or equivalent<br>- Able to read and write in Thai and sign written informed consent form<br>- Able to attend all scheduled visits and to comply with all trial procedures.<br>- Healthy or medically stable, as established by medical history and physical examination. For individuals with medical conditions, symptoms/signs, if present must be stable, under control or unchanged for the past three months. If medication is used to treat the condition, the medication dose must have been stable for at least one month preceding vaccination.<br>- For female participants:<br>• Not breast feeding, non-pregnant (based on negative urine pregnancy test) and no plan to become pregnant up to Day 60.<br>• Women who are not surgically sterile (hysterectomy or tubal ligation) or post-menopausal for more than one year must be willing to use effective |

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| | contraceptive method to prevent pregnancy until Day 60 after vaccination. Effective methods include intrauterine device, hormonal contraceptives (oral, injectable, patch, implant, ring) or double barrier contraceptives (condom or diaphragm with spermicide). Women with credible history of abstinence may be enrolled at the discretion of the investigator.<br><br>Exclusion:<br>- Participation in another clinical trial involving any therapy within the previous three months or planned enrollment in such a trial during the period of this study.<br>- Hypersensitivity after previous administration of any vaccine.<br>- Having a history of H1N1, H3N2 or FluB infection within 3 months preceding enrollment to the trial<br>- Vaccination against influenza in the past 6 months preceding enrollment to the trial<br>- Receipt of any non-study vaccine within four weeks prior to enrollment or refusal to postpone receipt of such vaccines until after the Day 21 visit.<br>- History of bronchial asthma, chronic lung diseases, chronic rhinitis<br>- History of immunodeficiency state<br>- History of immunosuppression < 6 months prior to immunization<br>- History of anaphylactic or other allergic reactions to influenza vaccine or any vaccine component or excipient (e.g. gentamicin or thimerosal)<br>- History of Guillain-Barré Syndrome.<br>- Having acute infection with fever > 38 degree Celsius or noninfectious diseases (within 72 hours) preceding enrollment in the trial<br>- Volunteers who have been taking immunoglobulin products or have had a blood transfusion during past 3 months before the beginning of the trial or planned receipt of such products prior to the Day 21 visit.<br>- Current alcohol abuse or drug addiction that might interfere with the ability to comply with trial procedures<br>- Any condition that in the opinion of the investigator would pose a health risk to the subject if enrolled, or could interfere with the evaluation of the vaccine |
| Phase: | II/III |
| Study Duration | Approximately 1 year |
| Participation Duration: | About three to four months per participant |
| Description of Agent or Intervention: | The vaccine is a seasonal trivalent inactivated split virion influenza vaccine recommended for Southern Hemisphere in 2017 (consisting of A/Michigan/45/2015 (H1N1)pdm-09-like virus, A/Hong Kong/4801/2014 (H3N2)-like virus, and B/Brisbane/60/2008-like virus) produced by the Government Pharmaceutical Organization (GPO), Thailand. Each dose of Tri Fluvac contains a total of 45 |

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| | micrograms (μg) hemagglutinin (HA) per 0.5 ml dose (15 μg HA per strain per dose), to be administered by intramuscular (IM) injection. Tri Fluvac is manufactured and formulated into a multiple-dose vial vaccine (2 doses) using thimerosal at relatively low concentration as preservative (≤ 7.5 μg mercury/ dose). Each 0.5 ml dose of vaccine may contain residual amounts of ovalbumin (≤ 5.0 μg), formaldehyde (≤ 50 μg), tween 80 (≤ 250 μg), triton x-100 (≤5 μg) and gentamicin (not more than 0.05 μg). The vaccine should be administered as a single 0.5ml intramuscular injection, preferably in the region of the deltoid muscle of the upper arm. |
| Description of active comparator vaccine: | Licensed Influenza vaccine (seasonal trivalent inactivated split virion influenza vaccine recommended for Southern Hemisphere in 2017 (consisting of A/Michigan/45/2015 (H1N1)pdm-09-like virus, A/Hong Kong/4801/2014 (H3N2)-like virus, and B/Brisbane/60/2008-like virus) 0.5 mL administered intramuscularly (IM) in the deltoid muscle of the non-dominant arm. |

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## 2. BACKGROUND INFORMATION AND SCIENTIFIC RATIONALE

### 2.1 Influenza virus and the target vaccine viruses

The influenza virus belongs to the virus family Orthomyxoviridae (2). They are single-stranded RNA viruses enclosed in a helical nucleocapsid. The envelope of influenza viruses are made up of two proteins found on its surface - hemagglutinin and neuraminidase, responsible for binding and cleaving off from the host cell, respectively (2). The influenza virus is easily transmitted from person to person (3). There are 3 types of seasonal influenza viruses - A, B and C. Type A influenza viruses are further classified into subtypes, of which influenza A(H1N1) and A(H3N2) subtypes together with Type B influenza viruses are currently circulating among humans (3). Type C influenza virus causes a relatively mild disease and no vaccine against it has been developed.

### 2.2 Influenza infections, disease burden and epidemiology

Seasonal influenza is a significant public health problem affecting all populations. According to the WHO, there are about 3 to 5 million annual cases of severe influenza illness, resulting in 250,000 to 500,000 deaths worldwide (3). Globally, the annual attack rate is estimated to be 5%-10% in adults and 20%-30% in children (3). A study by *Levy et al* (2015) showed that in Thailand, the influenza virus circulates year round with a peak usually observed during and immediately after the rainy season, which could have either a direct or indirect effect on the seasonality of influenza (4). The predominant strains of influenza virus was observed to be pH1N1 as the dominant strain in Thailand co-circulating with H3 and influenza B virus in 2014 (4). Influenza infections can lead to complications such as pneumonia. In Thailand, the influenza virus was identified in 1,346 (10.4%) of pneumonia cases affecting all ages. Of these, 702 (52%) were children <15 years of age (5). Vaccination is an effective way of preventing infections caused by influenza viruses (6). Moreover, it has been proven to be both beneficial and an essential public health intervention tool globally (7) . To minimize the disease burden, vaccination against seasonal influenza every year particularly to individuals at high risk for developing serious complications from influenza infection, and their close contacts remains a priority (8). As part of the national security program for self-reliance in vaccine production, the GPO entered a program targeting the development of an inactivated influenza vaccine called Tri Fluvac.

### 2.3 Non-clinical investigations

Non-clinical studies using animal models to assess the toxicity, immunogenicity and effectiveness of inactivated influenza vaccines have been reported (9). For instance, the study in ferrets showed that seasonal trivalent inactivated influenza vaccine (IIV) elicits cross protection against the 1918 Spanish Flu.

A toxicity study of GPO's Trifluvac in Sprague Dawley Rat was conducted by Syngene International LTD, India (Study Number: S14037). The results showed that after two doses (day1 and day22) of intramuscular administration (0.5 mL/animal), Tri Fluvac (2012 Strain Southern Hemisphere) did not induce any vaccine related effects on morbidity or mortality, systemic clinical signs, body temperature changes or visible local signs of skin reaction at the injection site, body weight changes, food consumption, food conversion efficiency, hematology, coagulation, clinical chemistry and urinalysis parameters, change in the organ weights and gross pathology of both sexes either in the main groups or the recovery groups. The microscopic observations of inflammatory reactions at the injection site and lymphoid hyperplasia of popliteal lymph node were considered as intended inflammatory and immunological response to the vaccine injection and, hence, were interpreted as non-adverse (10).

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The immune response in animal demonstrated that all of the treatment group animals had seroconversion compared to the negative control group. All animals had post vaccination HI titers ≥10 against Flu B and ≥40 against Flu A. In regards to the gender aspect, female rats seemed to be more sensitive to the vaccine than male as the HI titer and GMT obtained from female rats was higher than those obtained in male rats at the same bleeding time and sample concentration (11).

**2.4 Past clinical experiences**

According to the US Centers for Disease Control and Prevention (CDC), vaccination with seasonal inactivated influenza vaccine (IIV) is safe for both adults and children (12). In adults, the local reactions include mild pain and other injection site reactions after vaccination with IIV (12). A study by Bridges et al (2000) among healthy adults aged 18-65 years found that sore arm was significantly more common in vaccine recipients compared to placebo (53% vs. 18% [p<0.001], respectively for study years 1997-1998, and 53% vs. 22% [p<0.001], respectively for study years 1998-1999) (13). Additionally, redness at the injection site was reported more often by vaccine recipients (14% for study years 1997-1998, and 16% for study years 1998-1999) than placebo recipients (6% for study years 1997-1998, and 8% for study years 1998-1999), p<0.001) (14). Other studies in healthy adults also found sore arm to be more common among vaccine recipients (63.8% [14], 50.4% (15)) than placebo recipients (24.1% (16) [14], 14.2% (15)), p<0.001. Systemic reactions include headache (27.5%), muscle ache (13.5%) and fever (7.6%) in healthy adults who received IIV (15).

Oculo-respiratory syndrome (ORS) associated with IIV was identified in Quebec, Canada in 2000 (17) . Adults aged 40-59 years are most frequently affected (17). The symptoms are usually mild and resolve quickly without treatment (14). There has been a significant decline in reported rates of ORS per 100,000 doses from 46.6 in 2000 to 34.2, 20.6 and 9 in 2001, 2002 and 2003, respectively (17).

Serum antibody titers are the most common immune responses measured in vaccine studies. Serum HI antibody titers induced by the inactivated influenza virus vaccine correlates with protection (18, 19). Several studies have been conducted to evaluate the safety and immunogenicity of IIV in adults. For instance, the study by *Jackson et al* (2010) showed that IIV is immunogenic in healthy adults aged 18-49 years (20). Another study in healthy adults aged 18-48 years by Ohmit et al (2008) found a ≥ 4-fold increase in haemagglutination-inhibition antibody titer to influenza viruses i.e. 76.5% of subjects to the H3N2 vaccine strain, 74.7% to the H3N2 variant that circulated in 2005-2006 (p<0.001), 51.6% to the A/H1 vaccine strain (p<0.001), and 57.2% to the type B vaccine strain (15). Moreover, IIV also appeared to be well-tolerated and induced immune responses in children. (21-26).

A large population-based study in the US assessed the safety of IIV in 251,600 children aged <18 years during 1993-1999. This study did not find any increase in adverse events following vaccination with IIV (27). Another study among 791 healthy children aged 1-15 years found that 12% of vaccine recipients developed post vaccination fever (27). It was mild and self-limited.

From phase I/II trial of Tri Fluvac vaccine, 382 volunteers were screened for eligibility, out of which only 300 were enrolled. Out of the 300, 200 volunteers were given the vaccine while 100 volunteers were given placebos. Our results revealed that 30/100 placebo volunteers and 69/200 vaccine volunteers had experienced at least one adverse effect. There were altogether 34 and 95 events reported in placebo and vaccine groups, respectively. Of all the 129 events, 122 events were reported to not be related with the investigational products. Two events in the vaccine group

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suspected as AE related to treatment were reported as upper respiratory infection and headache. However, most of the AEs reported were mild while 4/100 were reported as moderate in the placebo group and 2/200 and 1/100 were reported as severe in the vaccine and placebo groups, respectively. All severe events were resolved. In addition, no fever was reported in either the placebo or vaccine groups for the entire 90 days study duration. However, mild cases of pain were observed with 32.5% and 19% for the vaccine and placebo groups, respectively. Similarly, swelling was also reported in 2.5% and 2% of the vaccine and placebo cases, respectively.

Furthermore, the table below (Table 1) summarizes the antibody titers obtained from the vaccine and placebo groups for the duration of the trial. As can be seen, for Flu A H1 and H3 titers, significant increases were observed in the vaccine group following immunization at days 21 as compared to the placebo group. Similarly, significant increase in the vaccine group as compared to the placebo group was also observed for Flu B post immunization. Therefore, the vaccine appeared to be well tolerated as no major problems were reported and the immune responses from the vaccine were high.

**Table 1: Geometric Mean of Immune Response and Increase in titers between Vaccine and Placebo groups (ITT)**

| HI Assay | Follow-up Day Group | Study | GMT (95%CI) | 4-fold rising n (%) |
|---|---|---|---|---|
| **Flu A H1 antibody titer** | | | | |
| | Day 0 | Vaccine (N= | 19.39 (16.40 - 22.92) | - |
| | | Placebo (N= | 20.14 (15.90 - 25.52) | - |
| | | p-value = | 0.7967[2] | - |
| | Day 21 | Vaccine (N= | 392.60 (337.59 - 456.59) | 176 (88.00) |
| | | Placebo (N= | 20.00 (15.79 - 25.33) | 0 (0.00) |
| | | p-value = | < 0.0001[2] * | < 0.0001[1] * |
| | | p-value = | < 0.0001[2] * | < 0.0001[1] * |
| **Flu A H3 antibody titer** | | | | |
| | Day 0 | Vaccine (N= | 51.16 (43.43 - 60.27) | - |
| | | Placebo (N= | 44.38 (35.03 - 56.22) | - |
| | | p-value = | 0.3356[2] | - |
| | Day 21 | Vaccine (N= | 214.81 (183.77 - 251.09) | 107 (53.50) |
| | | Placebo (N= | 43.17 (34.20 - 54.49) | 0 (0.00) |
| | | p-value = | < 0.0001[2] * | < 0.0001[1] * |
| **Flu B antibody titer** | | | | |
| | Day 0 | Vaccine (N= | 9.97 (8.72 - 11.39) | - |
| | | Placebo (N= | 9.20 (7.77 - 10.90) | - |
| | | p-value = | 0.6674[2] | - |

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| HI Assay | Follow-up Day Group | Study | GMT (95%CI) | 4-fold rising n (%) |
|---|---|---|---|---|
| | | | 115.92 (97.60 - 137.66) | 173 (86.50) |
| | Day 21 | Vaccine (N= 200) | | |
| | | Placebo (N= | 9.40 (7.83 - 11.28) | 1 (1.00) |
| | | p-value = | < 0.0001[2] * | < 0.0001[1] * |

Note: [1] Overall p-value (2-sided) based on Chi-squared test

[2] Overall p-value (2-sided) based on Wilcoxon sum rank test

- *Significant differences
- GMT is Geometric mean titer
- ITT is Intent-to treat analysis

The overall goal of GPO's influenza vaccine project is to establish a robust national influenza vaccine production of both IIV and LAIV in Thailand with the capacity of 10 million doses of seasonal trivalent IIV with the capacity to switch and produce pandemic LAIV when a pandemic emerges. The Ministry of Public Health has set up a national immunization program in order to create a demand to guarantee a sustainable supply from the established industrial influenza vaccine production plant.

**2.5 Investigational vaccine background**

In general, seasonal influenza vaccines are trivalent, containing a mixture of influenza A and B strains thought most likely to circulate in the coming season. However, monovalent vaccines have been produced against candidate pandemic strains. It is a common practice to use reassortant strains for production that give high yields of the appropriate surface antigens. Reassortant strains for vaccine production have the surface glycoproteins (HA and NA) of the circulating epidemic virus but the internal proteins of a standardized production strain.

There are three types of inactivated vaccines, the whole virus vaccines, split virus vaccines, and subunit vaccines. In split virus vaccines, the virus has been disrupted by a detergent**.**

Tri Fluvac is a seasonal trivalent inactivated split virion influenza vaccine [A/Michigan/45/2015 (H1N1)-pdm09, A/Hong Kong/4801/2014 (H3N2), and B/Brisbane/60/2008 virus strains], produced by The Government Pharmaceutical Organization (GPO), Thailand. Each dose of Tri Fluvac contains a total of 45 micrograms (μg) hemagglutinin (HA) per 0.5 ml dose (15 μg HA per strain per dose).

Tri Fluvac is manufactured and formulated as a multiple-dose vial vaccine (2 doses) using thimerosal at relatively low concentration as a preservative (≤ 7.5 μg mercury/ dose). Each 0.5 ml dose of vaccine may contain residual amounts of ovalbumin (≤ 5.0 μg), formaldehyde (≤ 50 μg), tween 80 (≤ 250 μg), triton x-100 (≤5 μg) and gentamicin (not more than 0.05 μg).

The vaccine should be administered as a single 0.5ml intramuscular injection, preferably in the region of the deltoid muscle of the upper arm. The vaccine should not be injected in the gluteal region or areas where there may be a major nerve trunk. It should not be injected intravascularly. A

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needle of ≥1 inch is preferred to ensure sufficient penetration of the muscle tissue in some adults. It is recommended that small syringes (0.5ml or 1ml) should be used to minimize any product loss.

The vaccine should be stored at 2-8°C (in a refrigerator), not frozen and protected from light. Allow vaccine to reach room temperature and shake before use. Between uses, return the multi-dose vial to the recommended storage conditions between 2-8 °C and use within 24 hours. Do not freeze. Discard if the vaccine has been frozen (28).

**2.6 Potential risks and benefits of the study**

The investigational vaccine may cause severe allergic reactions (e.g. anaphylaxis) when administered to anyone with known history of severe allergic reactions to egg proteins (eggs or egg products), or to any component of the vaccine (e.g. gentamicin, thimerosal). Some subjects may experience systemic reactions such as increased fatigue, headache, dizziness/vertigo), fever, runny nose, pharyngitis, cough, arthralgia, myalgia, nausea/vomiting. As usual, these symptoms go away by themselves within 1-3 days. In extremely rare cases of high individual sensitivity allergic reactions could be observed. There is a small possibility that inactivated influenza vaccine could be associated with Guillain-Barré Syndrome (GBS), no more than 1 or 2 cases per million people vaccinated. This is much lower than the risk of severe complications from flu, which can be prevented by flu vaccine (http://www.cdc.gov/vaccines/hcp/vis/vis-statements/flu.html).

The efficacy of this Tri Fluvac vaccine has not been evaluated before. However, the virus compositions included in the vaccine correspond to 2017 strains recommended by WHO for Southern Hemisphere.

Collection of blood samples through venipuncture may also cause subjects some discomfort or pain, redness, selling and/or hardness at the puncture site. By participating in this study, subjects will be screened by qualified clinicians for health status and through laboratory testing. This screening will be free of cost to the subject and may provide important information to the subject on the subject's health status.

**2.7 Study benefits**

The findings from this study will add to the body of knowledge regarding the safety and immunogenicity of IIV in healthy Thai adults aged 18-49 years. Data from this study might be useful for health policy makers in formulating guidelines and recommendations for influenza vaccination in healthy Thai adults.

## 3. HYPOTHESIS, OBJECTIVES AND ENDPOINTS

**Study Hypothesis:**

A single dose of the GPO seasonal trivalent split, inactivated influenza vaccine will induce immune responses to each of the three vaccine antigens and will be non-inferior to active comparator vaccine.

- The upper bound of the two-sided 95%CI on the ratio of the GMTs ($GMT_{licensed\ vaccine}$/ $GMT_{GPO\ Tri\ Fluvac}$) should not exceed 1.5 for each of the three vaccine antigens.
- The upper bound of the two-sided 95% CI on the difference between the seroconversion rates ($Seroconversion_{licensed\ vaccine}$ - $Seroconversion_{GPO\ Tri\ Fluvac}$) should not exceed 10 percentage points for each of the three vaccine antigens.

**Study Objectives:**

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**Primary objective**

**Primary Immunogenicity**: To evaluate the immunological non-inferiority seroconversion rate and Geometric Mean Titre (GMT) of the GPO seasonal trivalent split, inactivated influenza vaccine compared to active comparator vaccine for each of the three vaccine antigens at three weeks after immunization (Day 21).

**Primary Safety**:

To evaluate the safety profile of a single intramuscular dose of the GPO seasonal trivalent split, inactivated influenza vaccine in adults 18 to 49 years of age.

To compare the solicited symptoms, AE and SAE between subjects who will receive GPO's trivalent split, inactivated influenza vaccine and those who will receive an active comparator vaccine.

**Secondary objective**

To evaluate the HI responses at 3 weeks after immunization in participants with or without pre-existing HI antibody

**STUDY ENDPOINTS:**

**Primary endpoint**

**Primary Immunogenicity Endpoints and analysis:**

- Number and percentage of participants with seroconversion against each of the three vaccine antigens. Seroconversion is defined as a serum HI antibody titer meeting the following criteria:
  - Pre-vaccination titer <1:10 and a post-vaccination titer measured on Day 21 of ≥1:40; or
  - Pre-vaccination titer ≥1:10 and at least a four-fold increase in post-vaccination measured on Day 21.
- Geometric mean titers (GMTs) of serum HI antibodies pre- (Day 0) and post-vaccination (Day 21) for each of the three vaccine antigens.

**Primary Safety Endpoints:**

The number and proportion of participants reporting the following events will be assessed:

- Solicited local adverse events, including redness / erythema, swelling / induration, pain, and limitation of arm movement within 30 minutes of vaccination and over the 3-day period post-vaccination (Days 0-3).
- Solicited systemic adverse events, including fever, fatigue/malaise, muscle aches, joint aches, chills, nausea, and headache within 30 minutes of vaccination and over the 3-day period post-vaccination (Day 0-3).
- Unsolicited Adverse Events (AEs) occurring within 90 days post-vaccination.
- Serious Adverse Events (SAE) occurring during the entire study period (Days 0-90).

**Secondary Immunogenicity Endpoints and analysis:**

- Number and percentage of participants with a HI antibody titer ≥1:40 (seroprotective level) to each of the three vaccine antigens measured on Day 21 and Day 90.

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- Number and percentage of participants who develop at least a four-fold increase in HI antibody titers to each of the vaccine antigen post-vaccination measured on Day 21 and Day 90 segregated by pre-vaccination HI antibody titers (<1:10 or ≥1:10).
- Geometric mean fold rises (GMFRs) of serum HI antibodies (post-vaccination/pre-vaccination) for each of the three vaccine antigens.
- GMTs of serum HI antibodies pre- (Day 0) and post-vaccination (Day 21 and Day 90) for each of the three vaccine antigens segregated by pre-vaccination HI antibody titers (<1:10 or ≥1:10).
- GMFRs of serum HI antibodies (post-vaccination/pre-vaccination) for each of the three vaccine antigens segregated by pre-vaccination HI antibody titers (<1:10 or ≥1:10).

## 4. STUDY DESIGN:

### 4.1 Study Design

This is a phase II/III, non-inferiority double-blinded, randomized, and controlled trial to evaluate the safety and immunogenicity of a single dose the GPO seasonal trivalent inactivated influenza vaccine in male and female adults, ages 18 to 49 years old. Participants will be randomized 2:1 to one of two treatment allocations: 630 to vaccine, 315 to comparator. The study will be double blinded, meaning the study participants, investigators, and the sponsor will be unaware of the treatment allocated to each participant until the clinical trial database is declared final and locked.

All participants will be consented for participation and screened for eligibility through medical history review and physical examination. All volunteers will be checked against the inclusion/exclusion criteria. The screening assessments will be performed up to 30 days prior to the first vaccination. The screening procedures for the study including a medical history, vital signs, and physical examination will be performed. A urine pregnancy test will be done in females on screening day, day 0 prior to vaccination. Female volunteers should avoid pregnancy from the screening visit until at least 60 days after the vaccination by using an effective birth control method. The baseline immune response will be performed on day 0 prior to vaccination. One dose of the investigational vaccine or comparator will be given by intramuscular route (preferred injection site will be the deltoid of the non-dominant arm) after blood collection for immunology assays. Total follow-up period is 90 days for immune response and safety.

There will be 4 clinical visits and 1 phone visit as follows:

- Screening Visit (Day -30 to Day 0) Sign informed consent form, screen for eligibility (medical history review and physical examination)
- Day 0 (can be the same day with screening day): Vaccination day, subjects will remain at the clinic for at least 30 minutes for observation of any reactogenicity after vaccination. A diary card will be provided to the subjects for recording such events for 3 days after vaccination (Day 0-3).
- Day 7 (-3, + 7days): Return the diary card and report any adverse events that occur during the first seven days after immunization. Concomitant medication information will be collected.
- Day 21 (+7 days): Blood specimen collection for immune response, follow-up and report any adverse events.
- Day 60 (+14 days): Phone visit for reports of adverse events and IMI, if any.

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- Day 90 (+7 days): Blood specimen collection for immune response, follow-up and reports of any AEs/SAEs.

Blood specimens will be collected on Day 0 prior to vaccination, Day 21 and Day 90 following immunization. Serum samples will be separated from whole blood samples for HI assays. Subjects will be asked to report any adverse events and influenza-like illness (ILI) that occur after immunization. Concomitant medication will be collected. At Day 60, there will be a reminder call for reporting any adverse events and ILI. In addition, a throat or nasopharyngeal swab for influenza virus will be performed in those reported ILI. The study schedule and activities are summarized below in Table 2.

Safety will be assessed in all participants through Day 90. The justification for the three month follow-up, rather than six month follow-up is that: 1) in general, the safety of inactivated influenza vaccines is well-established, 2) the phase 1/2 trial showed very limited reactogenicity and no association with unsolicited adverse events.

Immunogenicity will be assessed by HI in a representative subset of at least 586 participants who received vaccine and 293 who receive comparator. In order to select the participants to test in an unbiased way, baseline and post-vaccination blood will be obtained from all the participants. An unblinded statistician will prepare a list of samples to be tested based on a random selection of participants, however neither the laboratory nor the clinical investigators will know the treatment received for each participants.

The study will test a seasonal TIV composed of the following strains:

- A/Michigan/45/2015 (H1N1)pdm-09-like virus
- A/Hong Kong/4801/2014 (H3N2)-like virus
- B/Brisbane/60/2008-like virus

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**Table 2: Study Schedule and activities**

| Procedures | Study Day | | | | | |
|---|---|---|---|---|---|---|
| | D0 | | D7 (-3, +7) | D21 (+7) | D60 (+14) | D90 (+7) |
| | Screening [e] | Immunization [e] | | | | |
| Informed consent | X | | | | | |
| Assessment of entry criteria | X | (X)[f] | | | | |
| Medical history, AE/SAE, Concomitant medication | X | (X)[f] | X | X | X | X |
| Vital signs | X | (X)[f] | X | X | | X |
| Urine pregnancy test [a] | X | (X)[f] | | | | |
| Physical examination [a] | X | (X) | (X) | (X) | | (X) |
| Immunization | | X | | | | |
| Diary card [b] | | X (Day 0-3) | X | | | |
| Blood for Immune response (HI Assay) (3ml) | | X | | X | | X |
| Phone call visit [c] | | | | | X | |
| Influenza subtype by RT-PCR[d] | | | (X) | (X) | (X) | (X) |

Remark

a. Only at screening, the rest when the history suggested [(x) = Optional as indicated by medical history].

b. Diary card will be provided to the subjects for recording reactogenicity for 3 days after vaccination (Day 0-3) and return to review at Day 7.

c. At Day 60, adverse events and influenza-like illness (ILI) will be followed-up by phone call.

d. Determination of influenza subtype by RT-PCR will be done when the ILI is confirmed [(x) = Optional as indicated].

e. Screening day can be the same day as immunization day (D0)

f. Will be done if immunization is not performed on screening day

(x) Optional

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## 4.2 Rationale of Study Design

Inactivated influenza vaccine has a well-established safety profile having been prescribed to millions of individuals globally, including children, the elderly, pregnant women, and individuals with chronic disease and immune suppression. Inactivated influenza vaccine also has well established international guidance including quantification of antigen, manufacturing, testing specifications for final bulk and final products, and requirements for national control authorities [30]. Because of predictable immunogenicity, dose finding studies of traditional, non-adjuvanted inactivated influenza are often not required. Furthermore, an immunogenicity study in lieu of an efficacy study as measured by HI (the surrogate endpoint) are common practice for inactivated influenza vaccines.

## 4.3 Study sites

This study will be conducted at Vaccine Trial Centre or its mobile sites, Faculty of Tropical Medicine, Mahidol University.

## 4.4 Study Product Descriptions

### *4.4.1 Acquisition*

GPO will provide both the study vaccine and comparator for this trial. The comparator is a licensed inactivated influenza vaccine.

The investigator or qualified designated staff member will be personally responsible for vaccine receipt and management. GPO will determine with the investigator or the designated staff member, the date(s) and time(s) of delivery of vaccine to the study clinic. Study vaccine, manufactured by GPO, and comparator will be supplied to the study clinic by GPO under controlled temperature conditions.

### *4.4.2 Formulation, Packaging, and Labeling (Product name and Trademark)*

The seasonal TIV produced by GPO uses embryonated chicken eggs. This is a split virion, inactivated vaccine. The vaccine source strains are:

- X-275 reassortant of A/Michigan/45/2015 (H1N1)pdm-09
- X-263B reassortant of A/Hong Kong/4801/2014 (H3N2)
- BX-35 reassortant of B/Brisbane/60/2008

Each dose of Tri Fluvac contains a total of 45 micrograms (μg) hemagglutinin (HA) per 0.5 ml dose (15 μg HA per strain per dose). Tri Fluvac is manufactured and formulated as a multiple-dose vial vaccine (2 doses) using thimerosal at relatively low concentration as preservative (≤ 7.5 μg mercury/ dose). Each 0.5 ml dose of vaccine may contain residual amounts of ovalbumin (≤ 5.0 μg), formaldehyde (≤ 50 μg), tween 80 (≤ 250 μg), triton x-100 (≤5 μg) and gentamicin (not more than 0.05 μg).

The vaccine should be administered as a single 0.5ml intramuscular injection, preferably in the region of the deltoid muscle of the non-dominant arm. The vaccine should not be injected in the gluteal region or areas where there may be a major nerve trunk. It should not be injected intravascularly. A needle of ≥1 inch is preferred to ensure sufficient penetration of the muscle tissue in some adults. It is recommended that small syringes (0.5ml or 1ml) should be used to minimize any product loss.

The vaccine should be stored at 2-8°C (in a refrigerator), not frozen and protected from light.

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Allow vaccine to reach room temperature and shake before use. Between uses, return the multidose vial to the recommended storage conditions between 2-8 °C and use within 24 hours. Do not freeze. Discard if the vaccine has been frozen.

### 4.5 Comparator

The comparator will be provided in prefilled, single dose, disposable syringes.

| | |
|---|---|
| Brand Name | A commercially available, licensed vaccine |
| Common or Non-Proprietary Name of Drug Substance | Influenza vaccine (split virion, inactivated) |
| Dosage Form(S) and Strength(s) | Suspension, Each 0.5-ml dose contains 15 µg of haemagglutinin (HA) of each of the following three influenza virus strains recommended for southern hemisphere 2017<br>• An A/Michigan/45/2015 (H1N1) pdm09-like virus<br>• An A/Hong Kong/4801/2014 (H3N2)-like virus<br>• A B/Brisbane/60/2008 –like virus |
| Route(s) of Administration | Intramuscular injection |
| Country from which the clinical supplies were obtained for the Lot to be Used in this Clinical Trial | Thailand |
| Market status in the above mentioned country | Market Approval |

### 4.6 Dosage, Preparation, and Administration of Study Products

#### *4.6.1 Dosage and Schedule*

A single dose level of the GPO Tri Fluvac will be evaluated in this study. The dose will be a total of 0.5 mL containing at least 15 mcg HA for each component. The vaccine is to be delivered intramuscularly preferably into the deltoid of the non-dominant arm.

#### *4.6.2 Precautions and Warnings*

- The GPO Tri Fluvac is only to be used for healthy adults 18 to 49 years of age participating in this study who meet the inclusion/exclusion criteria. It is forbidden to use the vaccine for any other purpose.
- Strict compliance with Thai regulations on the use of vaccines and biologicals is required.
- Vaccination should be intramuscularly into the deltoid of the participant's non-dominant arm. The dominant arm may be used if the participant prefers it or if the non-dominant arm would make it difficult to interpret the reactogenicity (for example, tattoo or scar).
- Study product syringes that have had temperature excursions may not be used. Contact GPO for further instructions.
- Only health workers who have been trained for this research study may administer study

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product to enrolled participants, assuring proper intramuscular injection technique and sterile injection.

- Only one person may be injected with one needle and syringe.
- Study participants must remain in the clinic and be monitored for 30 minutes after vaccination.
- The study vaccination clinic should have adequate facilities for monitoring and treating any reactions. Drugs to treat anaphylaxis must be available, as must specialist doctors for such an emergency. Prompt referral to additional needed facilities must be available.

### *4.6.3 Preparation and Administration*

An unblinded staff will prepare and administer vaccine to each participant. None of the unblinded staff will be involved in any reactogenecity and other safety evaluations.

To prepare and administer study product, vaccination facilities and investigators must comply with any applicable regulations. The step-by-step instructions for the investigator (or delegated staff) are as follows:

- Wash hands or use gel disinfectant. Prepare the study vaccine/placebo, needles, syringes, and sharps safety box ahead of time.
- Specific study procedures will be developed and include selecting the appropriate study product. Careful records must be maintained to ensure and document that each participant receives the correct product.
- Make sure sufficient equipment is available to provide every participant with a safe injection and to dispose of injection materials safely.
- Make sure emergency drug and equipment kits are available in both the vaccination area and the observation area.
- Greet the participant in a friendly manner. Ask whether he/she has any questions or concerns about injection and respond to his/her questions and concerns in a truthful and pleasant manner.
- Confirm the participant identity.
- Ensure the participant is seated or lying down.
- Inform the participant that everyone will be preferably vaccinated in the deltoid of their non-dominant arm.
- Put on gloves.
- Instruct the participant to put the hand on the hip and show them the deltoid.
- Disinfect the skin at the injection site.
- Inject intramuscularly the entire contents of the syringe into the deltoid region of the participant's non-dominant arm.
- While the plunger is still depressed, remove the needle from the participant's arm.
- Apply cotton swab with pressure to the injection site.
- Dispose of needle and syringe as one unit in a sharps container that is only used for this study.

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- Record the date of vaccination and vaccine vial number on the participant's vaccination record.
- Ask the participant to rest for 30 minutes.
- Blinded staff will provide the diary card, ruler, thermometer and explain how to use them for recording symptoms. Remind them of upcoming phone calls/visits.
- For 30 minutes following vaccination, observe the participant and ask about the participant's well-being.
- Before the participant leaves, review with them when to seek medical assistance if adverse events occur that require medical evaluation and treatment.

**4.7 Modification of Study Product for a Participant**
There is no dose adjustment for the product in the study.

**4.8 Accountability Procedures for Study Product**
The study vaccine and comparator will be kept in a secure place in cold storage at the study clinic segregated from other products, under a lock (the refrigerator or the room where product is stored) and with controlled access. During the study, the investigator or the person in charge of research product management will record information related to the delivery of study product 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 both, the used and the unused vials to GPO after completing the study, if directed. 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, the Principal Investigator or qualified designated staff member must contact GPO to get further instructions. The investigator must receive the written consent from GPO before clinical trial products can be used.

**4.9 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, GPO and trial monitors.

**4.10 Concomitant Medications/Treatment**
Concomitant medications for the treatment of pre-existing medical condition, and per AEs / SAEs reporting period outlined in Table 2 will be documented throughout the course of the study.

Treatment of conditions that are not exclusionary should continue, if needed by the participant. 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 using these products through Day 60. Use of such products will be recorded in the CRF.

**4.11 Unauthorized Products**
The following products are not authorized to be used during the study:

- Any concomitant medicine or biologic specifically prescribed for the treatment of a condition which is an exclusion criterion for participation in the trial.
- All non-study vaccines or biologics (including blood product) before Day 21.

Other concomitant products are allowed

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Participants will be educated not to take analgesic or antipyretic drugs in a preventive way as such medications might change the reactogenicity profiles of the study vaccine and comparator. However, the participants may take antipyretic drugs after injection, in order to treat any related symptoms.

## 5. Study Enrollment and Withdrawal

### 5.1 Study Participants, Source of Participants

This trial will enroll 945 male and female adults age 18 to 49 years. Participants will be recruited by referral, by word-of-mouth or other study materials, which will be approved by the ethical committee. The study staff will follow inclusion/exclusion criteria to determine eligibility. Screening evaluation will be conducted on all individuals interested in joining the study who have signed the study consent form. Results of the screening evaluation will be reviewed with each participant, regardless of eligibility.

### 5.2 Participant Inclusion/ Exclusion Criteria

(1) Inclusion Criteria

All participants must meet all of the following criteria to be considered eligible to participate in the study:

- Age 18-49 years old on the day of screening, having Thai ID card or equivalent
- Able to read and write in Thai and sign written informed consent form
- Able to attend all scheduled visits and to comply with all trial procedures.
- Healthy or medically stable, as established by medical history and physical examination. For individuals with medical conditions, symptoms/signs, if present must be stable under control or unchanged for the past three months. If medication is used to treat the condition, the medication dose must have been stable for at least one month preceding vaccination.

For female participants:

- Not breast feeding, non-pregnant (based on negative urine pregnancy test) and no plan to become pregnant up to Day 60.
- Women who are not surgically sterile (hysterectomy or tubal ligation) or post-menopausal for more than one year must be willing to use effective contraceptive method to prevent pregnancy until Day 60 after vaccination. Effective methods include intrauterine device, hormonal contraceptives (oral, injectable, patch, implant, ring) or double barrier contraceptives (condom or diaphragm with spermicide). Women with credible history of abstinence may be enrolled at the discretion of the investigator.

(2) Exclusion Criteria

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

- Participation in another clinical trial involving any therapy within the previous three months or planned enrollment in such a trial during the period of this study.
- Hypersensitivity after previous administration of any vaccine.
- Having a history of H1N1, H3N2 or FluB infection within 3 months preceding enrollment to the trial
- Vaccination against influenza in the past 6 months preceding enrolment to the trial
- Receipt of any non-study vaccine within four weeks prior to enrollment or refusal to postpone receipt of such vaccines until after the Day 21 visit.
- History of bronchial asthma, chronic lung diseases, chronic rhinitis
- History of immunodeficiency state

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- History of immunosuppression < 6 months prior to immunization
- History of anaphylactic or other allergic reactions to influenza vaccine or any vaccine component or excipient (e.g. gentamicin or thimerosal)
- History of Guillain-Barré Syndrome.
- Having acute infection with fever > 38 degree Celsius and noninfectious diseases (within 72 hours) preceding enrollment in the trial
- The volunteers who have been taking immunoglobulin products or have had a blood transfusion during past 3 months before the beginning of the trial or planned receipt of such products prior to the Day 21 visit.
- Current alcohol abuse or drug addiction that might interfere with the ability to comply with trial procedures
- Any condition that in the opinion of the investigator would pose a health risk to the subject if enrolled, or could interfere with the evaluation of the Vaccine

## 5.3 Treatment Assignment Procedures

### *5.3.1 Randomization Procedures*

This is a double-blind, randomized, and controlled trial with two groups: vaccine and comparator. Each participant will be assigned a unique screening number assigned by the investigator after signing the informed consent. After an individual is determined to be eligible for study participation, the participant will be randomized by assigning a unique participant identification number from the randomization schedule.

The complete randomization schedule that contains the participant identification number and the corresponding randomization assignment will be produced using computer software prior to the initiation of the study. The permuted randomized block design procedure will be used to generate the randomization schedules using varying block sizes. Treatment assignments will be completely randomized within each block, and the blocks will be ordered (permuted) randomly to ensure treatment balance during enrollment and maintenance of the blind.

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

Once a participant identification number has been assigned, it will not be used again. Additional participants may be randomized into the study in the case of any participant who is randomized but does not receive any study vaccine. Study participants will be randomly assigned to one of the two treatment groups. Blinding through randomization number will be maintained for the investigator who assesses immunogenicity and safety.

An un-equal randomization of 2:1 (Group V : Group C) lists will be generated by an independent statistician at the Center of Excellence for Biomedical and Public Health Informatics (BIOPHICS) at the Faculty of Tropical Medicine. The computerized randomization will be generated as a block of 3. The sample size of 945 (630 Group V: 315 Group C), the randomization numbers will be generated for 166 blocks. However, with the consideration of any unusual events that might unexpectedly happen during the trial, an extra 4 blocks will be generated as a backup set for replacement. This extra list will be kept separately and will be used only when necessary. The randomization will be kept in secured safe-box at BIOPHICS and will be opened only when needed. Only designated person will be able to get access to this randomization codes. However, complete

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randomization blocks of treatment materials will be sent only to the study coordination center for study vaccine preparation and distribution to study sites. All other study investigators as well as the volunteers will be blinded from the randomized codes. The codes will be open at the study conclusion or upon special request due to unexpected adverse event occurs. The emergency unblinding process will be done only when there is a special request for ethical and emergency clinical concerns by the sponsor or ethical committee or the principal investigator.

### *5.3.2 Blinding and Unblinding Procedures*

The randomization will be conducted by an organization or individual not involved in day to day the conduct of the study. The investigator will assign the unblinded staff responsible for vaccine preparation, administration, handling and accountability and to ensure that blinding is protected throughout the study procedures and no other site personnel involved in the conduct of the study has access to the information. After assessment of eligibility of a new subject, the Subject Number will be assigned to each subject sequentially in the order they are enrolled. The unblinded staff will prepare and administer vaccine/comparator according to randomization list provided by BIOPHICS. The unblinded staff will be responsible to keep the randomization list in a safe, locked and secured place with no access by other site personnel until the database is locked.

The randomization lists will be provided to GPO for them to label the study vaccine and comparator syringes and then placed in a sealed envelope immediately afterward. 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 overseeing ethics committee.

The vial labeling will be done at GPO before study vaccine and comparator are shipped. Study product injected into each participant will be recorded on the Case Report Form (CRF) using the exact allocation code for each product received by each participant.

The allocation codes link treatment identification with each participant identification number. These will be maintained in a secure location, by an individual not involved in the conduct of the study. If the investigator determines that it is necessary to unblind a participant, for example because a participant experiences an SAE possibly related to receipt of study treatment, then the treatment allocation to the participant will be communicated to the investigator.

## 5.4 Withdrawal/Discontinuation

### *5.4.1 Withdrawal conditions*

The volunteers have the right to withdraw from the trial at any time and for any reason. The researcher has a right to withdraw persons in case of occurrence of inter-current diseases, adverse reactions and the persons committing gross violation of the trial rules, for administrative or any other reasons, eg. lost to follow up, move from study area, in jail etc.

All interested parties understand, that excessive number of withdrawals can result in improper interpretation of the trial results, therefore it is necessary to avoid unreasonable decisions. It is necessary to avoid withdrawals, nevertheless, we understand, that they can take place during the trial. However, irrespective of the volunteer withdrawal period and reason, the final assessment of the trial concerning these participants should be made. The decision to withdraw a volunteer in connection to absence at the trial procedures should be made by the researcher only after finding-out of all circumstances. Given these factors and the importance of collecting full safety data from

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all participants, the reasons for terminating from the study should be minimal, but may include the following:

- Participant withdraws consent.
- PI decides that termination is in the best interest of the participant.
- The sponsor terminates the study.
- The targeted number of participants has been reached.

The decision to withdraw a volunteer in connection to presence of intercurrent disease or adverse reactions should be documented in the case record forms.

### *5.4.2 Procedure for Withdrawal/Discontinuation volunteer*

The investigator or study coordinator must notify the SPONSOR and to the WHO focal point immediately when a participant has been discontinued/ withdrawn due to an adverse experience (email or telephone or FAX). When a subject discontinues/withdraws prior to study completion, all applicable activities scheduled for the final study visit should be performed at the time of discontinuation. Any adverse experiences which are present at the time of discontinuation/withdrawal should be followed in accordance with the safety requirements.

Note: For participants who discontinue/withdraw prior to completion of the last visit, final visit procedures will be applied.

### *5.4.3 Procedure of replacement of the withdrawn volunteer*

No replacement plan for this study.

### *5.4.4 Strategies to Maintain and Recruit Additional Participants*

This is a relatively short trial with only one injection and 4 planned study visits per participant. Strategies to maintain retention in the trial include treating them respectfully, making sure they understand the study and potential side effects, and close communication with each participant about how the study unfolds. Given the short duration of the trial and anticipated minimal side effects of the study vaccine, participant withdrawal and loss of follow-up is expected to be low.

## 5.5 Lost to follow up

In the case of subjects who fail to return for a follow-up visit, documented reasonable efforts (i.e., documented telephone calls or certified mail) should be undertaken to locate or recall them, or at least to determine their health status while fully respecting their rights. These efforts should be documented in the source documents and CRF.

# 6. Termination of the Trial

## 6.1 End of Trial According to the Protocol

The end of the trial is defined as the date of the last contact of the last participant participating in the trial, according to the trial scheme.

## 6.2 Suspension and/or Premature Termination of the Trial

The trial may be prematurely terminated if the subject experienced disability or severe adverse event or death and such event is definitely related to study vaccine in the investigator's opinion. Furthermore, the Data Safety Monitoring Board (DSMB) judge to terminate the trial. The trial

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might be suspended at any time by GPO or the Thai FDA, any ethical review committee overseeing this study (for that institution only), or by the investigator (for his or her site only) for any safety concern. This includes, for example, and without limitation, an SAE resulting in death or an unusually high rate of SAEs. The Sponsor can terminate the trial for any reason which may not relate to safety of the volunteers. However, volunteers will be continued to follow for safety.

In the event of new data that indicate an increased level of risk to enrolled participants, the clinical trial will be suspended until GPO, the Thai FDA and all ethical review committees have reviewed relevant data and agreed that the trial may continue.

## 7. Study Schedule; Description of Visits

### 7.1 Recruitment

After getting approval from the Ethic Committee and before the start of the trial, the study team will inform the interested subjects about the study by word of mouth from existing pool of volunteers or through the recruitment materials which have been approved by Ethics Committee prior to use which will be distributed in the community health campaign.

A contact address and phone number will be provided for the interested subjects to call for more information about the study. Subjects who are interested in participating will be scheduled for a formal briefing and the informed consent process. The interested subjects will present at the clinical site on the day assigned. The clinical site will also accommodate “walk-ins”.

Prior to inclusion into the vaccine study, each participant will undergo medical history interview and general physical examination. Because screening procedures are required to assess eligibility, they will be performed only after consent is obtained. The Principal Investigator or designee will record the identity (IDs) of all participants who enter screening; whether they entered the trial or failed screening, and the reason for screen failure will be recorded on the screening/enrollment log.

### 7.2 Study Visits: Screening Visit

Screening: At the screening visit, prior to perform any study specific procedures, the Investigator and/or designated staff must provide all information related to the study to the subjects. Subjects must have enough time to read the Informed Consent Forms which have been approved by an Ethics Committee and ask questions. If the subjects are interested to participate in the study, they shall sign and date in the Informed Consent Form thereafter. The investigator or delegate who involves in the consent process shall check the completion of the consent forms and then sign and date on the same day of signing by the subject. A copy of the signed informed consent form will be given to each participant for his/her records.

After signing of informed consent form, all subjects will be screened for eligibility through medical history review and physical examination. All volunteers will be checked against the inclusion/exclusion criteria.

The screening assessments will be performed up to 30 days prior to the first vaccination.

The screening procedures for the study included a medical history, vital signs, and physical examination will be performed. A urine pregnancy test will be done in females. Female volunteers should avoid pregnancy at least 60 days after the vaccination by using an effective birth control method. They will be provided pregnancy counseling and the contraceptive pills or injection will be offered for free. Participants who meet eligibility criteria will be enrolled. 3 ml blood samples will be collected prior to vaccination.

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**7.3 Vaccination** (can be the same day as screening day): A single dose of a seasonal trivalent inactivated split virion influenza vaccine [A/Michigan/45/2015 (H1N1) pdm09-like virus, A/Hong Kong/4801/2014 (H3N2)-like virus, and B/Brisbane/60/2008-like virus] in GPO Tri Fluvac and comparator will be given to all subjects after blood collection for immunology assays. The vaccine will be administered via the intramuscular route; the preferred injection site will be the deltoid of the non-dominant arm. After vaccination volunteers will remain at the clinic for at least 30 minutes to observe for any reactogenicity after immunization. A diary card will be provided to the subjects for recording such events for 3 days after vaccination (Day 1-3).

At this visit; Repeat urine pregnancy tests will be performed if the immunization day is not the same as the screening day

1. The participant will be asked to complete the dairy card for 3 days, starting in the next day after injection, reporting any local or systemic reactions experienced and medications taken. The record of reactogenicity at 30 minute after immunization will be done at the clinical site.
2. The participant will have been instructed that if he/she experiences an AE requiring medical care, the participant should inform the investigator as soon as possible and seek medical care as appropriate. If the participant visits a health care provider, the participant 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. The participant should obtain in writing the names of medications prescribed by the health care provider.

**7.4 Follow-up visits**

***7.4.1 Day 7(-3, +7 days) after Injection: Return the diary card***

Subjects will return to the clinic on day 7 to return the diary card and report any adverse events. Subjects will be asked to report any adverse events that occur during the first seven days after immunization. Concomitant medication information will be collected.

At this visit;

1. Study staff will confirm participant identity.
2. Study staff will review the participant diary card and interim history with the participant and inquire about any new medical events since medical histories were last updated. Any AEs that have occurred and meeting reporting intensity will be recorded in the appropriate section(s) of the CRF. Diary card information will be entered into the CRF.
3. The participant will have temperature, pulse rate, and blood pressure recorded. A study clinician will perform a targeted (symptom based) physical examination and record the information on the CRF. Results will be reviewed by study staff and with the participant.
4. The participant will be instructed to inform the investigator as soon as possible if he/she experiences an AE requiring medical care and to seek medical care as appropriate. If the participant visits a health care provider, the participant 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.
5. There are no scheduled visits at week 2 after vaccination. Participants may be asked to come to the study clinic if the investigator follows up on any clinical issue. The participant will inform the study clinic of any medical events and seek medical care as needed. The participant will be instructed to give any health care provider they see the contact information for the investigator.

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### *7.4.2 Day 21 (+7 days): Blood specimen collection for immune response*

At this visit:

1. Study staff will confirm participant identity
2. Study staff will review interim medical histories and concomitant medications with the participant since they were last updated. Results will be recorded in the appropriate section of the CRFs
3. Blood specimen will be collected from all participants for immune response. Specimen collection information must be documented on the CRF and in specimen collection logs.
4. Study staff will ask about any medical event that would constitute an AE/SAE since the last visit.

### *7.4.3 Day 60 (+14 days): Follow up by phone call*

At this visit:

1. Adverse events and influenza-like illness (ILI) will be followed-up by phone call
2. Women who have agreed to use birth control for the study will be told that this is no longer required.

At Day 60, adverse events and influenza-like illness (ILI) will be followed-up by phone call.

### *7.4.4 Day 90 (+7 days): Final visit*

Day 90 is the last scheduled in-clinic visit.

At this visit:

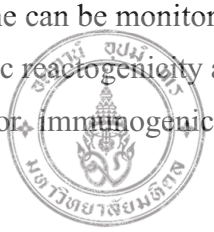
1. Study staff will confirm participant identity.
2. Study staff will review interim medical histories and concomitant medications with the participant since these were last updated. Results will be recorded in the appropriate section of the CRFs.
3. Blood specimen will be collected from all participants for immune response. Specimen collection information must be documented on the CRF and in specimen collection logs.
4. Study staff will ask about any medical event that would constitute an AE/SAE since the last visit.
5. 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.

After recording the information, the participant will be discharged from the study.

## 7.5 Early Termination Visit

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

1. Encourage the participant to stay in the study so that he or she can be monitored for safety.
2. The PI or clinician designee should review local and systemic reactogenicity and AEs.
3. The PI or clinician designee should obtain specimens for immunogenicity analysis, if withdrawal occurs prior to Day 21.



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4. Site staff should review Diary cad information with the volunteer, if the participant discontinues before Day 7.
5. The PI or clinician designee should examine the injection site and perform a symptom-based physical exam (PE), if indicated.

GPO must be informed within 48 hours of all instances of the premature termination in the trial.

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

### 7.6 Unscheduled Visits

Participants may present to the study center during operating hours for an unscheduled visit should they experience any AE, if the participant's condition requires medical intervention, or if a redraw of a blood sample is necessary and the participant agrees. Data for any examinations or other procedures performed on the participant at an unscheduled visit must be recorded on the appropriate CRFs.

For those participants who experience ILI symptoms, they will be asked to present themselves within 48 hours of flu like symptoms. Nasal swabs will also be taken for influenza diagnosis.

## 8. SAFETY AND LABORATORY EVALUATIONS

### 8.1 Safety Evaluations

All adverse experiences will be collected after the immunization throughout the period of the study. Such events will be recorded at each examination on the Adverse Experience Case Report Forms/Worksheets. Serious adverse experiences will also be collected and reported.

- Immediate reactions occurring within 30 minutes of vaccine administration
- Commonly occurring adverse events associated with vaccination, i.e., solicited adverse symptoms recorded during days 1-3.
- All other adverse events (including unsolicited events) occurring throughout the period of the study

An adverse experience is defined as any unfavorable and unintended change in the structure, function, or chemistry of the body temporally associated with the use of vaccine, whether or not considered related to the use of the product. Any worsening (i.e. any clinically significant adverse change in frequency and/or intensity) of a preexisting condition, which is temporally associated with the use of the vaccine, is also an adverse experience. The occurrence of an AE might come to the attention of study personnel during study visits and interviews of a study participant presenting for medical care. 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. Any medical condition that was present at the time that the participant 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

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**8.2 Solicited Local and Systemic Adverse Events**

Solicited adverse events are pre-specified local and systemic adverse events that are common or known to be associated with vaccination and that are actively monitored as indicators of vaccine reactogenicity. Investigators will not be required to assess causality of solicited adverse events if the onset is during the solicitation periods. If a solicited adverse event progresses beyond the solicited period, it will continue to be reported as a solicited adverse event. If the solicited adverse event occurs after the solicitation period, it will be reported as unsolicited AEs.

For this trial, solicited local and systemic AEs will be assessed by study staff 30 minutes after vaccination then daily for three days by the participants. Participants will be provided with a thermometer, ruler, and diary card to record the presence or absence of solicited AEs, severity of the solicited AE, and use of concomitant medication. The severity of the solicited local and systemic adverse events will be graded using the Toxicity Table for Grading Adverse Events (Appendix A). The specific solicited local and systemic adverse events that will be reported for this trial are:

Solicited local adverse event (at site of injection):

- Erythema/redness—based on size in cm.
- Swelling/induration (hardness at site of injection)—based on size in cm.
- Pain (pain with or without touching the injection site).
- Limitation of arm movement

Systemic Reactions:

- Fever—taken orally by thermometer
- Fatigue/malaise
- Generalized muscle aches
- Joint aches
- Chills
- Nausea
- Headache

**8.3 Unsolicited Adverse Events**

Unsolicited adverse events are any AEs that occur any time after the vaccine/comparator is given (temporally related to study product), whether or not deemed "related" to the product, and are not solicited (specifically asked of the participant). Unsolicited AEs can be observed by study staff while the participant is at a clinic for a study visit or reported by the participant at any time. Any sign or symptom that would normally be considered a "solicited AE" (for example, fever, nausea, injection site pain) starting after three days post-vaccination will be recorded as an unsolicited AE.

**8.4 Serious Adverse Events**

A serious adverse experience is any adverse experience occurring at any dose that:

- † Results in death; or

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- † Is life threatening (places the subject, in the view of the investigator, at immediate risk of death from the experience as it occurred [Note: This does not include an adverse experience that, had it occurred in a more severe form, might have caused death]; or
- † Results in a persistent or significant disability/incapacity (substantial disruption of one's ability to conduct normal life functions); or
- † Results in or prolongs an existing inpatient hospitalization (hospitalization in defined as an impatient admission, regardless of length of stay, even if the hospitalization is a precautionary measure for continued observation) (Note: Hospitalization [including hospitalization for an elective procedure] for a preexisting condition which has not worsened does not constitute a serious adverse experience); or
- † Is a congenital anomaly/birth defect (in offspring of subject taking the product regardless of time to diagnosis); or
- † Is a cancer; or
- † Is an overdose (whether accidental or intentional). Any overdose whether or not associated with an adverse experience must be reported within 24 hours to The Government Pharmaceutical Organization following appendix B. Standard Operating Procedure Reporting of Serious Adverse Event, and to WHO focal point

Also: Other important medical events that may not result in death, not be life threatening, or not require hospitalization may be considered a serious adverse experience when, based upon appropriate medical judgment, the event may jeopardize the participant and may require medical or surgical intervention to prevent one of the outcomes listed previously (designated above by a †).

**8.5 AE/SAE Reporting Period and Parameter**

Safety events are reported from the time of study injection (Day 0) through completion of the study at Day 90. Specifically, solicited AEs to assess local and systemic reactogenicities will be collected at 30 minutes and then daily for 3 days thereafter. If a solicited AE started during the 3 days post-vaccination and continues beyond the 3 days it will continue to be reported as a solicited AE. Unsolicited AEs and SAEs will be reported from Day 0 through the end of the study at Day 90.

**8.6 Severity of Adverse Events**

An investigator who is a qualified physician, will evaluate all adverse experiences as to:

- **Maximum intensity:**
  - Grade 1: Mild: is awareness of sign or symptom, but easily tolerated;
  - Grade 2: Moderate: is discomfort enough to cause interference with usual activity;
  - Grade 3: Severe: is incapacitating with inability to work or do usual activity.
  - Grade 4: Life threatening: is at immediate risk of death from the reaction as it occurred

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.

Grading of reporting temperature are referred to DAIDS Table in Appendix A (II)

| | |
|---|---|
| 0 (no) | < 38 °C |
| 1 mild | 38.0 °C - <38.6 °C |
| 2 (moderately high) | ≥38.6 °C - <39.3 °C |
| 3 (high) | ≥39.3 °C – <40.0 °C |

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| | |
|---|---|
| 4 (Potential Life Threatening) | ≥40 °C |

Other systemic reactions will be assessed in 4 scales as follow:

| | |
|---|---|
| 0 - no | No symptoms |
| 1 -mild | Symptoms, no significant interference with daily activity |
| 2 -moderate | Symptoms, affecting normal daily activity |
| 3 -severe | Symptoms markedly affecting normal daily activity |

At the same time, the following systemic symptoms are assessed

- Fatigue/ malaise
- Headache
- Chill
- Arthralgia
- Myalgia
- Nausea
- Vomiting

Women who become pregnant during the study period will be followed for safety until the end of the pregnancy or until the end of the study, whichever is longer.

**Adverse Event of Special Interest (AESI)**

AESIs are AEs that are considered by the Investigator to be relevant for the monitoring of the safety profile of the investigational vaccine.

*Potential indicators of oculo-respiratory syndrome (ORS): ORS was first noted to be associated with influenza vaccination during the 2000-2001 influenza immunization campaign in Canada and has since been reported in association with seasonal inactivated influenza vaccination as well. This acute post-vaccination syndrome presents with symptoms such as bilateral conjunctivitis (red eyes), facial swelling and respiratory symptoms (chest tightness, coughing, a sensation of throat closure, difficulty swallowing, hoarseness, wheezing or difficulty breathing). As the symptoms can mimic an allergic reaction, clinical investigators need to be aware of how to distinguish the two conditions as much as possible.

ORS occurring within 7 days after vaccination will be considered as AESI.

**8.7 Relationship to test vaccine (Did the test vaccine cause the adverse experience?):**
The determination of the likelihood that the test vaccine caused the adverse experience will be provided by an investigator who is a qualified physician. The investigator's signed/dated initials and date on the source document or worksheet, that supports the causality noted on the AE form, ensures that a medically qualified assessment of causality was done. This initialed document must be retained for the required regulatory time frame. The criteria below are intended as reference guidelines to assist the investigator in assessing the likelihood of a relationship between the test vaccine and the adverse experience based upon the available information.

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An adverse event's relationship to study medication assessment must be made by a medically qualified principal investigator or sub-investigator. The principle investigator or sub-investigator making relationship assessment must document this assessment in the subject's chart or file. The assessment of Causality is reported according to the investigator's best clinical judgment.

- "Related" should be selected if there is evidence of exposure to the test vaccine and the temporal sequence of the AE onset relative to administration of the test vaccine is reasonable. The AE is more likely explained by the test vaccine than by another cause. The AE shows a pattern consistent with previous knowledge of the test vaccine or test vaccine class. Or the AE could have been due to another equally likely cause.

- "Not related" should be selected if the subject did not receive the test vaccine OR temporal sequence of the AE onset relative to administration of the test vaccine is not reasonable OR there is another obvious cause of the AE. OR there is another more likely cause of the AE.

- "Not related" should be selected for subject's with accidental overdose without an associated AE.

**8.8 Follow up of AE**

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

**8.9 General Guidelines for Recording AEs**

To improve the quality and precision of acquired AE data, the Principal Investigator or designees 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 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.

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- 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 for surgical or diagnostic procedures, the illness leading to the surgical or diagnostic procedure should be recorded as the SAE, not the procedure itself. The procedure should be captured 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.

**8.10 Unexpected Allergic Reactions**

Immediate Reactions (within 30 minutes)

All participants will be observed for 30 minutes after administration of study product, with appropriate medical treatment readily available in case of an anaphylactic reaction following the administration of 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 that meets the criteria for an SAE must also be documented on an SAE form.

Emergency medicines will be available at the study clinic to be ready to give first aid if any adverse reactions or events should occur among any participant participating in this research.

**8.11 Clinical evaluations**

***8.11.1 Vital Signs***

The vital signs in this study include temperature in degrees Celsius (recorded to the nearest 0.1 degree) by oral thermometer; blood pressure in millimetres of mercury; and heart rates in beats per minute, measured by automated device or manually.

***8.11.2 Medical History***

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

- Current or recent (within two weeks of enrollment) acute 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 six weeks before enrollment.
- Hypersensitivity of any kind, but particularly to vaccines and egg proteins.
- 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 active tuberculosis disease.
- Alcohol or drug abuse.
- Concomitant medications that are ongoing (including trade name, dosing, indications, start date).

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- For women, pregnancy, menstrual, and contraceptive history and/or history of surgical sterility.

### *8.11.3 Physical Examination*

General Physical Examinations

Qualified study clinicians will conduct a physical examination of all participants at S1. This physical examination will include the following:

- Recording of general appearance
- Physical examination of all organ systems. This includes the following:
    - Brief neurologic 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
        - blood pressure
        - pulse/heart rate

* Elevated blood pressure not greater than Grade 1 (Systolic ≥140-159 or diastolic >90-99) will not be considered to be exclusionary at screening unless judged to be clinically significant by the PI or clinician designee.

Targeted Physical Examination

The Targeted Physical examination (PE) focuses on symptoms reported by the participant and the presence or absence of local and systemic reactogenicity. If no symptoms are reported by the participant, the Targeted PE does not need to be performed.

### *8.11.4 Injection Site Examination*

Assessment of local Injection site reaction 30 minutes after vaccination will be done by trained

study personnel and graded for severity according to the toxicity grading table in Appendix A.

- Erythema /redness will be examined under proper lighting conditions and measured with a ruler if present.
- Swelling/induration will be examined by palpation and visual inspection under proper lighting conditions. The examiner may temporarily mark skin at margins of visible swelling/induration, then measure with a ruler the maximum diameter.
- Pain will be assessed by inquiring as to whether there is significant discomfort at rest.
- Limitation of arm movement of the injection site causes discomfort, impacts limb movement or daily activity.

## 8.12 Laboratory Evaluations

### *8.12.1 Clinical Laboratory Evaluations*

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Pregnancy Test

In order to rule out pregnancy, female participants with potential to become pregnant will be tested with a qualitative human chorionic gonadotropin (hCG) test on a urine sample. Such testing will be

done on Screening (S1)/ Vaccination (D0) day, before vaccination. If Day S1 and D0 vaccination are conducted separately, the urine pregnancy test must be repeated on visit Day 0 prior to vaccination. No injection of study product may be given to a woman with child-bearing potential without a negative pregnancy test being done or to any woman with a positive pregnancy test.

### *8.12.2 Immunological Assays*

Immunogenicity testing will be performed by the laboratory at the Vaccine Trial Centre (VTC) using validated assays performed with established protocols. Samples may be sent to an additional qualified international lab for additional testing of influenza antibodies, as needed.

Hemagglutination Inhibition Assay (HI assay)

The HI assay is the most frequently used serologic test for determining immunologic response to influenza vaccination. Serum specific antibody against each of the vaccine strains represented in the vaccine will be measured by HI assay, which has been validated.

The two serological criteria that are accepted as indicators that the vaccine induces anti-hemagglutinin antibodies in subjects reaching levels required to meet current definitions of seroconversion:

- Percentage of subjects with either a pre-vaccination HI titer <1:10 and post-vaccination titer ≥1:40 or pre-vaccination titer ≥ 1:10 and a minimum 4-fold increase in post vaccination titer
- Increase in geometric mean titer (GMT) of serum HI antibodies

These two parameters are also evaluated yearly in human clinical trials due to the annual update of seasonal influenza vaccine strain composition.

*http://ecdc.europa.eu/en/healthtopics/seasonal_influenza/vaccines/Pages/influenza_vaccination.aspx*

### *8.12.3 Preparation, Processing and Transport Specimens*

**Blood collection**

Throughout the study, 9 ml of blood will be drawn from each participant.

Day 0: prior to immunization, 3mlblood sample will be drawn for immune responses (HI Assay).

Day 21 and Day 90: 3 ml of blood sample will be drawn for immune responses (HI Assay) on Day 21 and 3 ml of blood will be drawn for HI assay on Day 90.

The blood that is left over after testing as specified in this study protocol may be used in the future for other immune response tests which are related to this vaccine and will not be used for commercial purposes. The remaining blood will be stored at the Faculty of Tropical Medicine, Mahidol University for 5 years, after that the left over specimen will be destroyed per Destruction of Infectious Material Guideline.

**Serum processing**

Serum samples will be separated from participant's blood specimens using centrifugation method. All serum samples will be stored at -20°C until used.

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### *8.12.4 Methods of immunological and virological analysis*

Hemagglutination inhibition assay (HI): Serum specific antibody against the vaccine strains (A/Michigan/45/2015 (H1N1)-pdm09, A/Hong Kong/4801/2014 (H3N2) and B/Brisbane/60/2008) will be determined using hemagglutination inhibition (HI) assay. Briefly, nonspecific inhibitors will be removed from serum by overnight treatment with receptor-destroying enzyme (RDE). RDE treated serum samples will then be serially 2-fold diluted in 96-well-V bottom plates starting at a dilution of 1:10, and 4 HA units of virus will be added. Control wells will receive phosphate-buffered saline (PBS) alone or PBS with virus in the absence of antibody. Following 30 min of incubation at room temperature, 50 ul of a 0.5% (v/v) of goose (for A/Michigan/45/2015 (H1N1)-pdm09 and B/Brisbane/60/2008)) and 0.75% Guinea pig (for A/Hong Kong/4801/2014 (H3N2)) erythrocytes will be added. The antibody, virus and erythrocytes will be gently mixed, and the results will be recorded after an incubation for 45-60 min at room temperature. HI titers will be recorded as the inverse of the highest antibody dilution that inhibited hemagglutination.

ILI investigations:

Nasal swab samples will be collected from subjects with ILI symptoms for the determination of influenza virus by polymerase chain reaction (PCR). Influenza subtypes will be further investigated by sequencing.

## 9. Safety Oversight

### 9.1 Data Safety Monitoring Board (DSMB)

The DSMB will monitor accumulating safety data from the trial, as well as aspects of trial conduct and criteria for altering its course on the basis of safety. Specifically, the DSMB has the responsibility to review safety and immunogenicity of the interventions during the trial. DSMB will make recommendations to the sponsor regarding subject safety and termination of the trial for toxicity. There will be DSMB meetings before initiation of the trial, after vaccination 50% of the participants and at the closeout. If either the DSMB Chair or the sponsor sees the need to call unscheduled meetings, then both parties will discuss the rationale and outcomes desired and call such a meeting.

### 9.2 Expedited Safety Review

Safety events listed below require expedited Safety Medical Team (SMT) review within 36 hours of submission of the safety information to data management and or SAE reporting system.

| Event and relationship to study agent as assessed by investigator | Severity Grade |
|---|---|
| SAE, related | All grades |
| Unsolicited AE, related | 4 |
| Local reactions – erythema or induration | 4 |

### 9.3 Study Safety Pause

During the expedited safety reviews, if the SMT identifies safety concerns that warrant a safety pause, the SMT will notify the sponsor. If a decision is made to pause the study, all enrolment will be held, pending consultation with the sponsor and or THAI FDA.

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GPO 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, GPO will inform the local principal investigators 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 participants enrolled in the study. The principal investigators will assist GPO in informing the responsible Institutional Review Board (IRB)/ethics committee and provide the reason for the suspension or termination. In case of premature study or study clinic closure, the monitor will conduct all activities as indicated in the close out monitoring visit.

**Stopping rules:**

The occurrence of one or more of the following criteria will automatically pause or halt further vaccinations in the study:

1. One or more subjects experience a serious adverse event (SAE) that is suspected to be vaccine related.
2. One or more subjects experience a grade 4 injection site reaction (such as necrosis or sterile abscess at injection site requiring surgical intervention) that is suspected to be vaccine related.
3. Ten or more subjects experience a grade 3 or greater reactogenicity event following vaccination that is suspected to be vaccine related.
4. Five or more subjects experience the same grade 3 or more clinical abnormality following vaccination that is expected to be vaccine related

## 10. SAFETY CONSIDERATION

### 10.1 Duration:

Record the start and stop dates of the adverse experience. If less than 1 day, indicate the appropriate length of time and units.

### 10.2 Immediate Reporting of Adverse Experiences to the SPONSOR

**Serious Adverse Experiences**

Any serious adverse experience, including death due to any cause, which occurs to any subject after immunization throughout the period of the study, whether or not related to the investigational product, must be reported within 24 hours from when the site become aware to the government pharmaceutical organization (GPO) following appendix B: standard operating procedure reporting of serious adverse event, and to the WHO focal point.

All vaccine-related serious and unexpected adverse experiences will be reported on an expedited basis to regulatory agency (ies) but will remain blinded.

The Sponsor is responsible for informing the Data and Safety Monitoring Board (DSMB) of the occurrence of any SAE observed in a trial subject. Detailed description including required information, methods and specific timeframe will be provided in the appendix B: standard operating procedure reporting of serious adverse event.

### 10.3 Reporting of Pregnancy

Women who become pregnant during the study period will be followed for safety until the end of the pregnancy.

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All female volunteers will be individual interviewed to ensure the reliable birth control method which included a sexual history and/or the last menstruation period (LMP) and they will be informed of the urine pregnancy test result either negative or positive.

**10.4 Possible risks, including preventive and alleviative measures**

The participants will receive single dose of a seasonal trivalent inactivated split virion influenza vaccine [A/Michigan/45/2015 (H1N1)-pdm09, A/Hong Kong/4801/2014 (H3N2), and B/Brisbane/60/2008 virus strains], produced by The Government Pharmaceutical Organization (GPO), Thailand. The administration of study vaccine may cause the subject pain, redness or swelling/edema at the vaccine injection site. Some subjects may experience systemic reactions such as increased fatigue, headache, fever, arthralgia, myalgia, nausea/vomiting and ORS*. As usual, these symptoms go away by themselves within 1-3 days. In extremely rare cases of high individual sensitivity allergic reactions could be observed. Collection of blood samples through venipuncture may also cause subjects some discomfort or pain, redness, swelling and/or hardness at the puncture site.

**Potential indicators of oculo-respiratory syndrome (ORS): ORS was first noted to be associated with pandemic H1N1 vaccination and has since been reported in association with seasonal inactivated influenza vaccination as well. This acute post-vaccination syndrome presents with symptoms such as bilateral conjunctivitis (red eyes), facial swelling and respiratory symptoms (chest tightness, coughing, a sensation of throat closure, difficulty swallowing, hoarseness, wheezing or difficulty breathing). As the symptoms can mimic an allergic reaction, clinical investigators need to be aware of how to distinguish the two conditions as much as possible.*

**10.5 Prevention and treatment**

All enrolled participants must be verified healthy by medical history evaluation, physical examination. Additionally, in order not to enroll pregnant woman, urine pregnancy test must be performed at the screening visit and prior to study vaccination.

At the follow up visit, the assessment of vital signs, physical examination (if indicated by history) and clinical follow up will be performed and all reported adverse events would be assessed. The study investigators will be experienced in monitoring and managing the safety of participants.

The investigator or other physician in attendance will administer therapy as clinically indicated. All adverse events will be followed until resolved, or until a stable situation has been reached. Adverse events that occurred during the study and which had not resolved at the last study visit will be followed until they have abated, or until a stable situation has been reached.

**10.6 Concomitant Medication**

Information regarding concomitant medication in association with an adverse event will be collected and recorded in the source document and CRF.

The information reported in the CRF for each medication will be limited to:

- Trade name
- Indication
- Dose/ Unit/ Route/ Frequency
- Start and stop dates

Homeopathic medication and contraceptives medication will be recorded in CRF.

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### 10.7 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 certain unanticipated problems to GPO, 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 and their reporting and resolution.

## 11. DATA MANAGEMENT AND STATISTICAL ANALYSIS

### 11.1 Study hypothesis

**Immunogenicity:** A single dose of the GPO seasonal trivalent split, inactivated influenza vaccine will induce immune responses to each of the three vaccine antigens, which are non-inferior to active comparator vaccine.

**Safety**: A single dose of the GPO seasonal trivalent split, inactivated influenza vaccine will be safe and well tolerated in adults 18 to 49 years of age.

### 11.2 Sample size calculation

The sample size calculation was planned for a ratio of 2:1 between GPO Tri fluvac and active comparator vaccine respectively. The SAS 9.4 statistical software, was used to calculate the sample size needed for the study under the assumption of a non-inferiority trial for binary outcome endpoint.

According to the EMA recommendations for the co-primary endpoints, the sample size calculation was basing on the following primary endpoints:

- The difference in seroconversion rate of active comparator vaccine and Seroconversion rate of GPO Tri Fluvac should not exceed 10 percentage points.
- The difference in natural log of mean antibody titer between active comparator vaccine and GPO Tri Fluvac should not exceed 0.405, which is equivalence to the margin for GMT ratio = 1.5.

The sample size calculation was calculated using parameters of the three strains of influenza under the study, including H1, H3, and Flu B. The estimates for seroconversion and standard deviation of natural log of antibody titer were obtained from previous study, phase II study of GPO Tri Fluvac.

| Influenza strain | Titer Visit | Treatment Group | Sero-conversion | Mean of ln(titer) | SD of ln(titer) |
|---|---|---|---|---|---|
| H1 | Day 21 | Vaccine | 0.88 | 5.9728 | 1.08277 |
| H3 | Day 21 | Vaccine | 0.535 | 5.36976 | 1.11926 |
| Flu B | Day 21 | Vaccine | 0.865 | 4.75286 | 1.23306 |

The sample size calculation for non-inferiority test for proportions was performed with the margin of 0.1, assuming different seroconversion rate of the three influenza strain, and expected difference in seroconversion of the two groups is 0.000 with one-sided test alpha level 0.025 and power 0.8. Finally the sample size was adjusted for 7% not included in the ATP cohort. The required sample size for this co-primary endpoint reached a total of 945 subjects: 630 for study vaccine group and 315 for comparator vaccine group.

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***Two group test of equivalence in proportions (large unequal n's)***

| | H1 | H3 | Flu B |
|---|---|---|---|
| **Test significance level, α (one- sided)** | 0.025 | 0.025 | 0.025 |
| **Standard proportion, $\pi_S$** | 0.880 | 0.535 | 0.865 |
| **Equivalence limit difference, $\pi_T - \pi_S$, $\Delta_0$** | 0.100 | 0.100 | 0.100 |
| **Test expected proportion, $\pi_T$** | 0.880 | 0.535 | 0.865 |
| **Expected difference, $\pi_T - \pi_S$, $\Delta_1$** | 0.000 | 0.000 | 0.000 |
| **Power ( % )** | 80 | 80 | 81 |
| **$n_S$** | 125 | *293* | 134 |
| **$n_T$** | 250 | *586* | 276 |
| **Ratio: $n_T / n_S$** | 2.000 | 2.000 | 2.000 |
| **$N = n_S + n_T$** | 375 | 879 | 414 |
| ***Adjusted 7% not included in the ATP cohort*** | | | |
| **$n_S$** | 134 | ***315*** | 148 |
| **$n_T$** | 268 | ***630*** | 296 |
| **$N = n_S + n_T$** | 402 | ***945*** | 444 |

The sample size calculation for noninferiority test comparing two means was performed according to the standard deviation of natural log scale of antibody titer of the 3 influenza strains with the margin of 0.405 (equivalence to ln of GMT ratio at 1.5), assuming expected difference in mean of natural log scale of antibody titer between the two groups is 0.000 with one-sided test alpha level 0.025 and power 0.8. Finally the sample size was adjusted for 7% not included in the ATP cohort. The required sample size for the co-primary endpoint reached 354 in total: 236 for study vaccine group and 118 for comparator vaccine group.

***Two group t-test of equivalence in means (unequal n's)***

| | H1 | H3 | Flu B |
|---|---|---|---|
| **Test significance level, α (one-sided)** | 0.025 | 0.025 | 0.025 |
| **Equivalence limit difference, $\Delta_0$** | 0.405 | 0.405 | 0.405 |
| **Expected difference, $\Delta_1$** | 0.000 | 0.000 | 0.000 |
| **$\Delta_0 - \Delta_1$** | 0.405 | 0.405 | 0.405 |
| **Common standard deviation, σ** | 1.082 | 1.119 | 1.233 |
| **Power ( % )** | 80 | 80 | 80 |
| **n1** | 85 | 91 | 110 |
| **n2** | 170 | 182 | 220 |
| **Ratio: $n_2 / n_1$** | 2.000 | 2.000 | 2.000 |
| **$N = n_1 + n_2$** | 255 | 273 | 330 |
| ***Adjusted 7% not included in the ATP cohort*** | | | |
| **$n_S$** | 91 | 98 | 118 |
| **$n_T$** | 182 | 195 | 236 |

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| | | | |
|---|---|---|---|
| $N = n_S + n_T$ | 273 | 293 | **354** |

Final sample sizes for the study after adjusted for 7% not included in the ATP cohort = *630:315*

With 630 evaluable participants randomized to GPO Trifluvac vaccine, the study has 95% power to detect at least one vaccine associated AE if true incidence is 1.0%. This provides high probability of detecting common (1–10%) vaccine associated adverse events. If no vaccine-related SAE is observed, the study will be able to exclude events occurring at approximately ≥0.58% based on the upper bound of the one sided 95% Confidence Interval (CI). The precision of the estimate of AEs judged to be related to vaccine as bounded by 95% CI is presented in Table 3.

**Table 3 Exact 95% Confidence Intervals around Potential Number of Study Drug Associated Adverse Events**

| Sample size | Number of events | Two sided exact 95% CI |
|---|---|---|
| 630 | 0 | 0 0.58 |
| | 1 | <0.01 0.88 |
| | 2 | 0.03 1.14 |
| | 5 | 0.25 1.84 |
| | 10 | 0.76 2.90 |

## 11.3 Data Analysis

### *11.3.1 General Data Analysis Considerations*

**Analysis Populations**

All subjects who receive one vaccination will be included in the safety population. This population will be used in the evaluation of safety and tolerability.

The immunogenicity analysis will be conducted based on an intent-to-treat (ITT) analysis. The population for the intent-to-treat analysis is defined as all individuals in the trial. The intent-to-treat analysis will include individuals who do not comply with the protocol-defined treatment schedule; that is, the intent-to-treat analysis will include individuals who may not complete the vaccination and follow-up.

As there might be some individuals who did not comply with the protocol-defined treatment schedule, a per-protocol analysis (PPA) will also be conducted. The population for the per protocol analysis is defined as individuals who meet all inclusion and exclusion criteria, and complete the treatment schedule.

**Data considerations**

All available data will be included in the data listings and graphical summaries. For the formal statistical analyses and summary statistics, all available data will be included as appropriate for the analysis methods. Procedure to account for missing, unused or spurious data will be defined in the

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final data analysis report. Any data transformation that may necessarily be done will also be described in the final study report.

***Assessment of immune response***

According to WHO and FDA guidelines, the antibody titres to corresponding vaccine strain of influenza virus will be analyzed by comparison of paired serums using HI assay.

The serum samples will be collected on Days 0 prior to vaccination, Day 21, and Day 90 and will be analyzed for presence of influenza-specific antibody using Hemagglutination Inhibition (HI) assay. HI antibody titers will be compared between pre- and post-vaccination serum samples.

Percentages of subjects with each immune response will be calculated along with 95% CIs using exact statistical methods. Geometric mean titers (GMTs) along with 95% CIs will also be calculated using the t-test. No multiplicity adjustment to the error rate, alpha, will be made.

The primary immunogenicity endpoint is based on the ATP cohort, and NI conclusion will be based on the outcome of this analyses.

The primary immunogenicity endpoints and analysis are as follows:

- Number and percentage of participants with seroconversion against each of the three vaccine antigens. Seroconversion is defined as a serum HI antibody titer meeting the following criteria:
    - Pre-vaccination titer <1:10 and a post-vaccination titer measured on Day 21 of ≥1:40; or
    - Pre-vaccination titer ≥1:10 and at least a four-fold increase in post-vaccination measured on Day 21.
- Geometric mean titers (GMTs) of serum HI antibodies pre- (Day 0) and post-vaccination (Day 21) for each of the three vaccine antigens.

In assessing the non-inferiority, the upper bound of the two-sided 95% CI on the difference between the seroconversion rates (Seroconversion rate of active comparator vaccine – Seroconversion rate of GPO Tri Fluvac) should not exceed 10 percentage points. For the other primary endpoint, the upper bound of the two-sided 95% CI on the ratio of the GMTs (GMT active comparator vaccine/GMT GPO Tri Fluvac) should not exceed 1.5.

In addition, the secondary immunogenicity endpoints and analysis include the following:

- Number and percentage of participants with a HI antibody titer ≥1:40 (seroprotective level) to each of the three vaccine antigens measured on Day 21 and Day 90.
- Number and percentage of participants who develop at least a four-fold increase in HI antibody titers to each of the vaccine antigen post-vaccination measured on Day 21 and Day 90 segregated by pre-vaccination HI antibody titers (<1:10 or ≥1:10).
- Geometric mean fold rises (GMFRs) of serum HI antibodies (post-vaccination/ pre-vaccination) for each of the three vaccine antigens.
- GMTs of serum HI antibodies pre- (Day 0) and post-vaccination (Day 21 and Day 90) for each of the three vaccine antigens segregated by pre-vaccination HI antibody titers (<1:10 or ≥1:10).

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- GMFRs of serum HI antibodies (post-vaccination/pre-vaccination) for each of the three vaccine antigens segregated by pre-vaccination HI antibody titers (<1:10 or ≥1:10).

### *11.3.2 Assessment of Safety data*

The number and percentage of subjects with solicited local and systemic reactions during the three days post-injection will be assessed. In addition, all adverse events (AE) and serious adverse events (SAEs), and new onset of chronic diseases (NOCDs) will be collected for the entire study period.

Specifically, the following safety parameters will be monitored and analyzed in terms of the number and proportion of participants reporting the following events will be assessed:

- Solicited local adverse events, including redness/erythema, swelling/induration and pain within 30 minutes of vaccination and over the 3-day period post vaccination (Day 0-3).
- Solicited systemic adverse events, including fever, fatigue/malaise, muscle aches, joint aches, chills, nausea, vomiting and headache within 30 minutes of vaccination and over the 3-day period post vaccination (Day 0-3).
- Unsolicited adverse events (AEs) occurring within 90 days post vaccination.
- Serious Adverse Events (SAE) occurring during the entire study period (Days 0-90).

### *11.3.3 Exploratory Analysis:*

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## 11.4 Analysis of Safety Endpoints

The safety profile of the GPO Tri Fluvac will be evaluated by the number and proportion of participants experiencing AEs by severity and relatedness to vaccination of the following five categories for all participants:

A. Solicited local adverse events, including redness / erythema, swelling / induration, pain within 30 minutes of vaccination and over a 3-day period (Day 0-3) post-vaccination.

B. Solicited systemic adverse events, including fever, fatigue, malaise, muscle aches, joint aches, chills, nausea, and headache within 30 minutes of vaccination and over a 3-day period (Days 0-3) post-vaccination.

C. Unsolicited AEs occurring within 90 days post vaccination.

D. SAEs occurring during the entire study period (Days 0-90).

Occurrences 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. Percentage of participants experiencing each reaction or event, or at least one reaction or event will be calculated along with two-sided exact 95% CIs. No statistical testing will be performed for unsolicited AEs; including SAEs. The percentage of participants with solicited AE and SAEs will be compared between vaccine and comparator groups and a two-sided p-value of 0.05 will be considered statistically significant.

## 11.5 Analysis of Immunogenicity Endpoints

Primary Endpoint:

The primary analyses of immune responses to the GPO Tri Fluvac 21 days post-injection will be performed based on According to Protocol (ATP) cohort by the following:

A. Number and percentage of participants with seroconversion against each of the three vaccine

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antigens post-vaccination. Seroconversion is defined as a serum HI antibody titer meeting the following criteria:

- Pre-vaccination titer <1:10 and a post-vaccination titer measured on Day 21 of ≥1:40, or
- Pre-vaccination titer ≥1:10 and at least a four-fold increase in post-vaccination measured on Day 21.

B. Geometric mean titers of serum HI antibodies pre- (Day 0) and post-vaccination (Day 21) for each of the three vaccine antigens.

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). If a titer is reported as greater or equal to the upper limit of the assay, it will be set to that limit.

Secondary Immunogenicity Endpoints:

The secondary immunogenicity endpoints will be analyzed by the following:

A. Number and percentage of participants with a HI antibody titer ≥1:40 (seroprotective level) to each of the three vaccine antigens measured on Day 21 and Day 90.
B. Number and percentage of participants who develop at least a four-fold increase in HI antibody titers to each of the vaccine antigen post-vaccination measured on Day 21 and Day 90 segregated by pre-vaccination HI antibody titers (<1:10 or ≥1:10).
C. Geometric mean fold rises (GMFRs) of serum HI antibodies (post-vaccination/ pre-vaccination) for each of the three vaccine antigens
D. GMTs of serum HI antibodies pre- (Day 0) and post-vaccination (Day 21 and Day 90) for each of the three vaccine antigens by pre-vaccination HI antibody titers (<1:10 or ≥1:10).
E. GMFRs of serum HI antibodies (pre- and post-vaccination) for each of the three vaccine antigens segregated by pre-vaccination HI antibody titers (<1:10 or ≥1:10).

The proportions of seroconversion responders, at Day 21 between groups (vaccines or comparator) will be examined and compared to determine the effect of an inactivated trivalent influenza vaccine. The antibody titers of each group will also be presented as GMT. The 95% CI and *p-value* will be calculated and presented. Multivariate analysis will be performed as needed to explore potential confounders.

## 11.6 DATA HANDLING AND RECORD KEEPING

The site PIs are responsible for ensuring the accuracy, completeness, and timeliness of the data reported. Data collection is the responsibility of the clinical trial staff at the study site under the supervision of the site PIs or designee. Data collection must be completed as soon as possible to allow for timely review of safety information. The BIOPHICS will be responsible for data management activities, including quality review, analysis, and reporting of the study data according to SOPs.

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### *11.6.1 Data Management Plan*

The BIOPHICS will be responsible for data management and analytic support for the trial. The data for study subjects will be recorded in Electronic Case Report Forms (e-CRFs). A data management plan developed by the BIOPHICS and approved by the study team will be implemented to cover procedures from handling completed e-CRFs to preparing clean datasets. The final dataset developed at the BIOPHICS will be the primary database for the trial.

The e-CRFs will be completed at the clinical trial sites and sent onto the US FDA compliant electronic data capture (EDC) system, so-called DF/Net, located at BIOPHICS on a daily basis. Then BIOPHICS data managers will compile the data records, perform data quality check and post QA/QC inquiry on the EDC system. This inquiry on data quality would be checked with the source document and revised within the e-CRFs by the clinicians and/or other responsible persons at the study sites. The correction process on e-CRFs will be finalized and confirmed as "clean" by the BIOPHICS data management team. The study progress and monitoring report for designated personnel at clinical trial sites and related co-investigators will be generated by BIOPHICS.

Standard Good Clinical Practices (GCP) will be used to insure the accuracy, consistency, and reliability of the data. The study will be monitored for compliance with FDA regulations and GCP guidelines by designated personnel. The quality of the data will be monitored by the data monitoring team.

Clean datasets will be prepared and analyzed by the BIOPHICS statistician who do not involved in the process of data management. The independent statistician will provide analytic summaries as per data analysis plan.

### *11.6.2 Source Documents*

Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.

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, printouts of data that were generated by technical equipment, and specimen collection logs. For many data fields, the paper worksheet will be the source document. All source documents must bear at least the participant identifier and the printing date (for data from recording device). The medical review of such records should be documented as necessary with signature or initials and date of the review.

For source data verification, the monitor (on behalf of the study Sponsor) must have direct access to source documents that support the data recorded, including medical records, original laboratory records, and Informed Consent Forms (ICFs). If source data are electronic, these data must be printed, signed and dated by the site PI or designee and stored in the participant's study file. Essential documents, including ICFs, must be filed and kept in the study files.

### *11.6.3 Database Locking Procedures*

A final database lock for the primary safety and immunological analysis will occur after all participants have completed all follow-up visits, including the Day 90 safety contact, review of the severity of any AEs has been performed and finalized, all data queries have been resolved to the satisfaction of the Sponsor, and monitoring is complete.

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### *11.6.4 Records Retention*

Study records for all study volunteers will be maintained by the investigator in a secure storage facility for at least 5 years after Thai FDA approval of a marketing application of the product.

## 12. Quality control and quality assurance

Each volunteer will be assigned a unique study identifier (Screening number to be used during screening and subject number to be used during vaccination and follow up). Only the subject number without initials will appear on CRFs. Stored samples will contain only subject number and date without initials. Name will not be used on any samples or any publication of this study. Subject identities will be available only to the study investigators and members of GPO for the purposes of conducting this study and complying with THAI regulations. All efforts will be made to protect the privacy of volunteers.

Source documents and Electronic Case Record Form (e-CRF) package will be kept in secure cabinet with limited access to designated person only. However, it is permitted for the study/clinical monitor and/or auditor, ethical committee and other regulatory agency to be able to do access the data as per their request.

## 13. Monitoring

The study will be monitored by qualified and appropriately trained person(s) appointed by GPO. In accordance with applicable regulations, GCP, GPO's standard operating procedures or designated monitor standard operating procedures, monitors will periodically contact the site and perform site monitoring visits.

Monitoring procedures will be followed, in order to comply with GCP guidelines. Direct access to the on-site study documentation and medical records must be ensured.

### 13.1 Monitoring Plan

Individuals qualified by education, training, and experience will carefully monitor the study. The extent, nature, and frequency of site 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. The Monitoring Plan will detail reporting requirements to GPO to keep it appraised of study progress. Representatives of GPO or its designees may participate in monitoring visits or visit the study clinic on its own to provide proper oversight.

### 13.2 Set-up Visit (Site Initiation)

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. Site Initiation will be performed to verify that:

- the staff have been trained on the protocol, all study procedures, and GCP
- study supplies are in place
- the site team is identified
- responsibilities are assigned by Investigator (delegation log)
- the study documentation is complete as per ICH-E6 Section 8 (list of essential documents before the start of the trial).

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### 13.3 Routine Monitoring Visits

Monitoring will be conducted according to an agreed upon Monitoring Plan. The study may use a

Risk Based Monitoring approach that will be targeted to issues most critical to the rights and welfare of study participants and the veracity and integrity of study data. The individuals responsible for monitoring the study will periodically review the progress of the study and should have access to all records necessary to 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:

- Assess if consent was properly obtained.
- Assess adherence to the protocol eligibility criteria.
- Look for evidence that randomization was followed.
- Look for evidence that blinding was maintained.
- Check on study conduct and documentation of procedures/assessments related to the study endpoints:
    - Specimens obtained correctly
    - Specimens labeled correctly
    - Specimens stored correctly
- Check on study conduct and documentation of protocol-required safety assessments, including SAEs.
- Ensure that there is documentation of withdrawals and deaths, and 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 the monitor to discuss findings and any 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 GPO or its designees to occasionally accompany the monitor during site visits.

**13.4 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 disposition of used and unused study products according to the instructions of the sponsor.
- Review of site study records for completeness.
- Ensure study data is handled according to instructions by GPO.

**13.5 Audits and Inspections**

For the purpose of compliance with applicable regulatory guidelines, GPO, its designees, or the national regulatory authority may conduct a site audit. This could occur at any time from site initiation to after conclusion of the study. If the national regulatory authority requests an inspection, the Principal Investigator must inform GPO immediately about this request.

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

## 14. Ethics/Protection of Study Participants

### 14.1 Ethical Standard

This study will be conducted in full conformity with any Thai regulations or guidelines for clinical trials and with the Declaration of Helsinki in order to ensure the best protection for study participants.

### 14.2 Insurance

GPO, the study sponsor, will have the task of obtaining insurance to cover treatment for study related injuries and other insurance as necessary to meet its ethical or regulatory obligations for conducting this study in Thailand. The insurance contract will be concluded between the "STUDY" and the insurance company prior to the beginning of the trial. The clinical insurance will be covered against legal liability imposed by operation of law to pay damages in respect of injury to any research subject caused by or arising out of participation by the research subject in the clinical trial. If there are any damages under the Clinical Trials Liability Policy, claim can be made to GPO Managing Director, telephone 02 2038208, 02 2038229 Fax: 02 3548850.

### 14.3 Compensation, assurance of Emergency Medical Care and Care for Adverse Events and other services

During the participation, the Sponsor shall be responsible for compensation to participants in the events of trial related injuries. The compensation for traveling costs, meal, and time lost will be provided to participant for 1,000 baht per visit.

Study participants will be observed by qualified clinicians after vaccination, and emergency care will be immediately available to participants who need it. Adverse events that occurred during the study and which had not resolved at the last study visit will be followed until they have abated, or until a stable situation has been reached. Subjects will receive medical care, as needed at The Hospital for Tropical Diseases, Faculty of Tropical Medicine, Mahidol University, Bangkok, Thailand. Depending on the event, follow-up may require additional tests or medical procedures as indicated, and/or referral to the general physician or a medical specialist. Most adverse events that are expected and non-emergent can be handled at the study clinic by the clinical staff as they occur at no cost to the participant. These would be events such as fainting or feeling lightheaded, or swelling from the injection of the study products or blood draws. For those who fail screening from abnormal lab value, the abnormality will be informed to the participants and will be referred/ treated accordingly.

### 14.4 Institutional Review Boards and Independent Ethics Committee

No research activities on participants will be conducted without having the study reviewed and approved by 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 Thailand as well as any other regulatory reviews required.

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The study clinic's institution maintains an institutional review board. This study will be reviewed and approved by each institution's IRB prior to submission to the THAI FDA. All amendments will be notified to Thai FDA after they have been approved by institutional IRB.

The PI or designee shall maintain copies of all application documents and forward copies of all IRB and IEC documents and approvals to GPO or its designee prior to the start of the study. The approval letters must identify all documents approved and list the study clinic, the study investigator, protocol title, version number, and date in addition to the ICF version number and date and the date of IRB or IEC approval. The PI will sign all approved versions of the protocol.

The PI 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 PI 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 participants or when the changes involve only logistical or administrative aspects of the study (e.g., change of telephone number, etc.).

GPO will report to the THAI FDA and the IEC/IRBs any new information related to the study vaccine which possibly affect the safety of participants or their risk/benefit ratio for participating in this trial.

The PI will be responsible for reporting to the IEC/IRBs when the clinical study has been completed.

**14.5 Informed Consent Process**

At the screening visit, prior to performing any study specific procedures, the Investigator and/or designated staff must provide all information related to the study to the subjects. Subjects must have enough time to read the Informed Consent Forms which have been approved by an Ethics Committee and ask questions. If the subjects are interested in participating in the study, they shall sign and date the Informed Consent Form thereafter. The investigator or delegate who is involved in the consent/assent process shall check the completion of the consent/ forms and then sign and date on the same day of signing by the subject. A copy of the signed informed consent form will be given to each participant for his/her records.

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

- Discussion with the participants regarding the purpose of research, the time and duration that the participants need to participate, the procedures involved in the study, the scientific evidence that justifies conducting this experimental trial in humans, and the potential risks and known benefits of participating in the research.
- Randomization and that participants will have about 2 in 3 chance of receiving the study vaccine.
- That the study staff will not know which study product the participant will receive and that the study staff and participant will have no way to choose which product is received by the participant.
- That the participant's participation is voluntary, and the participant's refusal to participate will not result in any fine or in any loss of rights or access to medical care that the

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participant is normally already entitled to receive.

- That in the event of unforeseen circumstances or needs, the investigator may decide to withdraw the participant from continued participation in the research even without the consent of the participant.
- That the participant will be provided with the results of any new important findings related to the trial or the study vaccine which may influence the participant's decision on whether to continue to participate in the research.
- That the participant will be told the number of other participants participating in the research.
- That the participant will be told who to notify as the point of contact with the investigator and IRBs in case the research participant would like to know more information regarding the trial and his/her rights as a research participant.
- That the investigator is responsible for collecting from the participant signed and dated written informed consent forms regarding participation in the study before the participant may participate in the research; that the participant will be given a signed and dated copy of the form to keep; and that the investigator must keep the original signed and dated informed consent form in the investigator's research files.

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

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. The participant 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.

If approved by the local ethics committee, participants will be informed that they will be compensated for travel to and from the clinic and for meals during study visits. This will be approved by the local ethics committee.

## 14.6 Participant Confidentiality

### *14.6.1 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 GPO or participant. 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 confidentiality.

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Medical information about individual participants 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 required by law. Confidentiality will be ensured by the use of study participant numbers for the identification of each participant; these study participant numbers will also be used for participant data in the participant files at the site and for the CRFs.

### *14.6.2 Confidentiality of Participant Records*

Participant confidentiality is strictly held in trust by the participating investigator and his or her staff. This confidentiality is extended to cover testing of biological specimens in addition to the clinical information relating to participating participants.

Study participants will not be identified by name on any data collection form or on any other documentation sent to GPO 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. Monitors will conduct periodic monitoring visits to ensure that the data are stored securely. Only study clinicians, study staff, monitors, or the Sponsor or its designee will be granted access to the study data and records.

The PI 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).

## 14.7 Sharing of Study Results

### *14.7.1 Sharing of Study Results with the Participant*

All results of clinical laboratory testing, if performed to evaluate an AE, will be reviewed with the participant. A copy of the laboratory report will be provided to the participant if requested.

### *14.7.2 Incidental Health Findings*

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

## 14.8 Future Use of Stored Specimens

Biological specimens will be maintained for five years to allow re-testing with newly developed assays for influenza or to assist with the development of new assays. The specimens will be maintained at the Vaccine Trial Centre (VTC). Specimens will not be labeled with any personally-identifying information. Participants do not have to agree to storage and future use of specimens to be in the vaccine study. In addition, they can change their mind and notify the study site for destruction of the specimens for that participant. When specimens are no longer needed, they will be destroyed.

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## 14.9 Potential Risks and How They are addressed

**Physical Risks**: The main risks of this study are risks of physical injury. Administration of study product may cause the participant immediate mild pain in the arm. Other side effects include pain and inflammation at the injection site or systemic symptoms such as fever and body aches. These are all explained to participants in the consent form.

Serious or allergic reactions also may be possible. This risk is addressed by trying to screen out people who have had an allergic reaction to vaccines in the past and who may have an allergy to one of the components of the vaccine. Should an allergic reaction occur with vaccination, the study clinic will follow its SOP for handling medical emergencies and have supportive medicines in place, in addition to trained staff.

Besides administration of study product, collection of blood specimens may cause some discomfort to participants. Venipuncture is sometimes associated with fainting, discomfort or pain, bleeding, bruising, redness, swelling, local hardness, and/or infection at the puncture site. This risk is addressed by having trained staff draw the blood.

Study participants will be observed closely by qualified clinicians and care will be immediately available to participants after vaccination, including emergency care, if needed. If additional urgent care or resources are needed, the participant 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 participant at no cost to the participant.

In the case of expected and unexpected reactions after the use of vaccines, study participants will receive appropriate medical care and treatment. GPO will ensure coverage for the cost of medical treatment and resolve these cases according to current regulations in Thailand.

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

- Monitoring of participants closely for 30 minutes after vaccination and providing emergency care for any immediate reactions.
- Monitoring of participants for adverse events which are not life-threatening
- Monitoring of participants for severe and serious adverse events

The study site can provide treatment for the reactions to the study product, which are likely to be pain, fever, redness, swelling, etc. Study site is trained to handle anaphylaxis and have the medications on site. If medical issues arise that cannot be managed by the clinic performing the study, the study doctor will refer the participant to care to an appropriate clinic within or outside of the institution. The cost will be covered by the public insurance in Thailand or by the clinical trial insurance obtained by GPO.

**Risks to Privacy:** Anyone participating in research using their real name and medical information can face a loss of privacy. These risks are mitigated by using unique IDs in place of a participant's name, restricting access to study information, and not naming or identifying a participant in any publication.

**14.10 Benefits to Study Participants**

Study participants may not benefit from being in the study, however, there is potential for some benefit:

- People may benefit from the physical exams that are done in the study, as it may reveal information about their health that they did not know before.

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- Being successfully immunized against the seasonal influenza virus can benefit the health of the participants and protect them during the flu season. Especially when the vaccine strains are matched.

## 15. Protocol Deviations

A protocol deviation is any noncompliance with the clinical study protocol or GCP. The noncompliance may be either on the part of the participant, the investigator, or the study clinic 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 GPO. Deviations 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 GPO in a timely manner after identification. The site should complete a Noncompliance Report to report all protocol deviations. The following types of noncompliance should be reported within 72 hours to GPO:

- Serious or continuing noncompliance, when that noncompliance:
    - Increased or had the potential to increase risks to research participants; or
    - Compromised or had the potential to compromise the welfare/well-being of participants; or
    - Decreased potential benefits to participants; or
    - Comprised the integrity of the research, including research data; or
    - Indicate a pattern that happened over a period of time, involved a number of research participants, or involved a variety of deviations.

These noncompliance events, specifically, will require expedited reporting within 72 hours to GPO and the site's ethics committee:

- Conducting research without ethics committee approval;
- Conducting screening/enrollment or other research procedures without proper consent, including using unapproved consent forms:
- Implementing changes to the research without ethics committee approval
- Deviating from the study requirements in a way that results in the *possibility* of increased risk to participants, for example:
    - Administering the wrong treatment
    - Omitting required safety monitoring
    - Not following the protocol re: requirements for privacy or confidentiality
    - Enrolling ineligibile participants.
- Using an outdated consent form with multiple participants;
- Collecting incomplete consent documentation from multiple participants (e.g., missing signatures and/or dates).
- Enrolling more than the approved number of participants than GPO or the site have agreed

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the site may enroll.

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.

To limit the potential for protocol deviations, the trial site will receive training (or retraining, as necessary) on protocol implementation and will operate according to written procedures. In addition, the Site PI and clinic coordinator will receive training in identifying unanticipated problems and noncompliance.

## 16. Human Resource for the Study

### 16.1 Human Resource for the Study

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

### 16.2 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.

## 17. Clinical Study Report and Publication Policy

### 17.1 Clinical Study Report

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

All data, documents, any 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 GPO.

Following completion of the clinical study report, the investigators, working with GPO and representatives, are expected to publish the results, negative or positive, of this research in peer-reviewed scientific journal(s). GPO may not prohibit the public dissemination of the results of this trial.

### 17.2 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 GPO/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**

## 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 Division of AIDS (Acquired Immuno-Deficiency) (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 Upper Limit of Normal (ULN) or lower limit of normal (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.

[1] Based On The DAIDS Table For Grading the Severity of Adult And Pediatric Adverse Events, Version 1.0, December, 2004; Clarification August 2009; and Guidance For Industry: Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials; FDA, 2007.

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## 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.

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| PARAMETER | GRADE 1 MILD | GRADE 2 MODERATE | GRADE 3 SEVERE | GRADE 4 POTENTIALLY LIFE- |
|---|---|---|---|---|
| **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 |
| **Fever** (non-axillary | 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) |

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| PARAMETER | GRADE 1 MILD | GRADE 2 MODERATE | GRADE 3 SEVERE | GRADE 4 POTENTIALLY LIFE-THREATENIN |
|---|---|---|---|---|
| **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 |
| **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 cm2 surface area AND Symptoms causing no or minimal interference with usual social & functional activities | ≥ 5 to < 10 cm in diameter OR ≥ 25 to < 100 cm2 surface area OR Symptoms causing greater than minimal interference with usual social & functional activities | ≥ 10 cm in diameter OR ≥ 100 cm2 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) |

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| PARAMETER | GRADE 1 MILD | GRADE 2 MODERATE | GRADE 3 SEVERE | GRADE 4 POTENTIALLY LIFE- |
|---|---|---|---|---|
| | | | | |
| **Injection Site Induration or Swelling** *Report only one*<br><br>*> 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* |
| **Injection Site Pruritus** | Itching localized to the injection site that is relieved spontaneously or | Itching beyond the injection site that is not generalized OR Itching localized to the | Generalized itching causing inability to perform usual social & | NA |

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## APPENDIX B: STANDARD OPERATING PROCEDURE REPORTING OF SERIOUS ADVERSEEVENT

**Research and Development Institute**
Standard Operating Procedure

*Restricted circulation*

| | |
|---|---|
| Group : Clinical Research Co-ordination Group<br>Title : REPORTING OF SERIOUS ADVERSE EVENT (SAE) | SOP No. : CC-001-01<br>Page No. : 1 of 8<br>Supersedes : CC-001-00<br>Effective From : 24 Feb 17<br>Review Period : 2 Years |

| Author(s): | Mr.Nava Suthepakul | | | |
|---|---|---|---|---|
| | Prepared By | Reviewed By | Reviewed By | Authorized By |
| Sign: | | | | |
| Name: | Mr.Nava Suthepakul | Mrs.Piengthong Narakorn | Ms.Wilak Vangkanonta | Dr.Nuntakan Suwanpidokkul |
| Date: | 23 Feb 17 | 23 Feb 17 | 24 Feb 17 | 24 Feb 17 |
| Designation: | Researcher of Clinical Research Co-ordination Group | Director of Clinical Research Co-ordination Group | Director of Research and Development QualityAssurance Group | Director of Research and Development Institute |

History of the SOP:

| Ver. No. | Reason for Revision / History | Effective date |
|---|---|---|
| 00 | • Revise format of SOP No. GPO/CT/SOP02, Revision No: 5.0 to SOP No.CC-001-00 due to administrative reason | 03 Mar 14 |
| 01 | • Periodic review<br>• To correct the time for SAE reporting from 'within 24 hours after the event' to 'within 24 hours after SAE has been acknowledged' | 24 Feb 17 |

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## 1.0 OBJECTIVE

To define the appropriate procedure for handling SAE arising during clinical study. Any information on serious, unexpected adverse drug reactions reports from the Site should be submitted on an expedited basis to Thai FDA by GPO Clinical Coordinator.

## 2.0 SCOPE

This SOP is applicable for Clinical Trials Phase I, II and III.

## 3.0 RESPONSIBILITY

The Physician on duty under the guidance of the Principal Investigator/ Clinical Investigator/Consultant Physician/ Medical Expert is responsible for the handling of the serious adverse events and its documentation.

The Principal Investigator is responsible for making necessary arrangements for administrative handling of the serious adverse events (arrangements for shifting the subject to the hospital, etc.) and for reporting to the Sponsor (through GPO Clinical Coordinator) and IEC/IRB.

GPO Clinical Coordinator is responsible for sending the SAE report received from the Site to Safety Medical Team (SMT) and the regulatory authority/ other authorities (if any).

## 4.0 BACKGROUND

It is important to take cautious action on important clinical safety information arising during clinical development. Thus, agreed definitions and terminology, as well as procedures, will ensure uniform Good Clinical Practice (GCP) standards. The provision of this SOP should be used to provide the appropriate procedure for handling SAE which is reported from the Site, evaluation of causality relationship and qualification of suspected, unexpected, serious drug reaction for expedited (rapid) reporting to Thai FDA. Causality assessment is required in all cases. All cases judged by either the reporting health care professional or the Sponsor as having a reasonable suspected causal relationship to the vaccine are qualified as ADRs.



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**Adverse Event (or Adverse Experience) (AE)**

Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment.

**Adverse Drug Reaction (ADR)**

All noxious and unintended responses to a medicinal product related to any dose should be considered adverse drug reactions.

**Unexpected Adverse Drug Reaction**

An adverse reaction, the nature or severity of which is not consistent with the applicable product information.

**A Serious Adverse Event (SAE) or reaction is any untoward medical occurrences that are any dose:**

1) Results in death,
2) Is life-threatening,

   Note: The term "life-threatening" in the definition of "serious" refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.
3) Requires inpatients hospitalization or prolongation of existing hospitalization,
4) Results in persistent or significant disability/incapacity,
5) Is a congenital anomaly/birth defect,

   or
6) Be a medically important event or reaction. This would include important medical events that may not be immediately life threatening or results in death or hospitalization but may jeopardize the patient/subject or may require intervention to prevent one of the other outcomes listed in the definition above.



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## 5.0 LIST OF ABBREVIATIONS

| | | |
|---|---|---|
| ADR (s) | : | Adverse Drug Reaction (s) |
| AE | : | Adverse Event (or Adverse Experience) |
| CRF | : | Case Report Form/Case Record Form |
| DSMB | : | Data and Safety Monitoring Board |
| FDA | : | Food and Drug Administration |
| GCP | : | Good Clinical Practice |
| GPO | : | The Government Pharmaceutical Organization |
| ICD | : | International Classification of Diseases |
| ICF | : | Informed Consent Form |
| ID No | : | Identification Number |
| IEC | : | Independent Ethics Committee |
| IRB | : | Institutional Review Board |
| ISF | : | Investigator Site File |
| N/A | : | Not Applicable |
| PI | : | Principal Investigator |
| SAE | : | Serious Adverse Event |
| SMT | : | Safety Medical Team |
| SOP | : | Standard Operating Procedure |
| SUSAR | : | Suspected Unexpected Serious Adverse Reaction |
| UNK | : | Unknown |
| WHO - ART | : | World Health Organization - Adverse Reaction Terminology |



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## 6.0 PROCEDURE

### 6.1 Initial SAE reporting from the Site within 24 hours

6.1.1 After SAE has been acknowledged, Principal Investigator (PI) or designate sends SAE notification to GPO Clinical Coordinator within 24 hours by e-mail with the minimal 5 elements below;

1) Identifiable patient

2) Investigational product

3) An event or outcome that can be identified as serious and unexpected, and for which, in clinical investigation cases, there is a reasonable suspected causal relationship.

4) Details on reporter of event

5) Project No./Title

6.1.2 GPO Clinical Coordinator sends the SAE notification received from the Site to SMT with copy to clinical monitor by e-mail within 6 hours.

### 6.2 The Principal Investigator concludes and sends signed Attachment No. 01 (SAE Report Form for Clinical Trial) to GPO Clinical Coordinator within 48 hours after the event.

6.2.1 GPO Clinical Coordinator fills and sends the received Attachment No. 01 (SAE Report Form for Clinical Trial) to SMT with a copy to clinical monitor and DSMB by scanned e-mail attachment within 24 hours.

6.2.2 Attachment No. 01 is archived in the Investigator Site File (ISF) and the Sponsor file.

### 6.3 Reviewing of SAE report and writing draft notification of Suspected Unexpected Serious Adverse Reaction (SUSAR) by SMT

6.3.1 Evaluation of causality relationship and expectedness by SMT.

6.3.2 If need clarification, SMT can directly communicate with PI with copy of the communication to GPO Clinical Coordinator.



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6.3.3 SMT writes causality assessment and decision on qualification for SUSAR in topic 35-37 of Attachment No. 01 (SAE Report Form for Clinical Trial) and sends signed Attachment No. 01 to GPO Clinical Coordinator within 72 hours by scanned e-mail. If SUSAR is justified, Attachment No. 02 (Thai FDA Format) is needed to fill by SMT.

6.3.4 GPO Clinical Coordinator submits signed Attachment No. 01 to PI within 24 hours and submits Attachment No. 02 to Thai FDA within 24 hours (if required).

6.3.5 All communications are archived in the Investigator Site File (ISF) and the Sponsor file.

**6.4 It is noted that timing for SAE report stated in this SOP (6.1-6.3) are expressed for SAE with fatal or life-threatening outcomes. For other SAEs, timing can be extended to be double of the time for SAE with fatal or life-threatening outcomes.**

**6.5 Qualification for SUSAR and writing final report of SUSAR by SMT.**

6.5.1 SMT must make a decision on qualification for SUSAR. If SUSAR is confirmed, SMT writes a final report of SUSAR and sends the signed report by scanned e-mail to GPO Clinical Coordinator within 5 days.

6.5.2 GPO Clinical Coordinator submits the final report of SUSAR within 3 days to Thai FDA, Investigator and DSMB and copies to clinical monitor.

6.5.3 For serious and unexpected ADR, SMT must decide if there is a need to unblind the case. Unblinding can be done as described in SOP: Emergency Unblinding of Randomization Code (SOP No. CC-002-XX).

6.5.4 The final report of SUSAR and the emergency unblinding form filled by SMT (if available) must be kept in the Sponsor file.

**6.6 Update of ICF by PI within 1 month.**

**6.7 Update of Investigator's Brochure by GPO within 1 month.**



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**6.8 SAE Reporting time frame for Thai FDA**

It is noted that timing for draft notification (Attachment No. 02) to Thai FDA expressed for SUSAR with fatal or life-threatening outcome must be within 7 calendar days after SAE has been acknowledged. The final report is subsequently submitted within additional 8 calendar days. All others non-fatal or non-life-threatening SUSAR, draft notification (Attachment No. 02) must be submitted within 15 calendar days after SAE has been acknowledged.

**6.9 Annual or Closeout Trial Safety Report**

6.9.1 SMT summarizes end of study safety report, line listing of all suspected serious ADRs and aggregate summary tabulation of all serious ADRs in Thai FDA format, and submits to Thai FDA within 5 months after the end of the trial.

6.9.2 GPO Clinical Coordinator submits end of study safety report to Thai FDA, within 1 week.

6.9.3 All communications must be kept in the Sponsor file.

**6.10 If other reportable events**

6.10.1 Other reportable events include: (1) accidental exposure, (2) cancer, (3) suicide, (4) misuse (abuse), (5) product defect, and (6) overdose. The reporting can be modified by using the same time frame and the same procedures as specified in 6.1 - 6.9.

**7.0 REFERENCES**

1. ICH E2A "Clinical Safety Data Management: Definitions and Standard for Expedited Reporting".
2. Thai FDA. Regulations and guidelines on report of Adverse Drug Reactions.
3. SOP No. CC-002-XX; "Emergency Unblinding of Randomization Code"


*Note: XX refer to current version of the SOP(s) mentioned above*

| | |
|---|---|
| Electronic File Name & Path: Q:\CC_Section\SOPs\SOP-CC\SOP CC-001\SOP CC-001-01\ SOP No. CC-001-01 | Reviewed By (CRCG) : <br> Date: 23 Feb 17 |

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## 8.0 ATTACHMENTS

| Sr. No. | Form No. | Title | No. of Pages |
|---|---|---|---|
| 01 | NA | SAE Report Form for Clinical Trial | 13 |
| 02 | NA | AE Report Form (Thai FDA Format) | 01 |

| | |
|---|---|
| Electronic File Name & Path: Q:\CC_Section\SOPs\SOP-CC\SOP CC-001\SOP CC-001-01\ SOP No. CC-001-01 | Reviewed By (CRCG) : Date: 23 Feb 17 |

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