CLINICAL STUDY PROTOCOL V118_18 Version 5

A Phase III, Randomized, Observer-Blind, Controlled, Multicenter Clinical Study to Evaluate the Efficacy, Safety and Immunogenicity of an MF59-Adjuvanted Quadrivalent Influenza Vaccine Compared to Non-influenza Vaccine Comparator in Adults ≥ 65 Years of Age

Phase III Efficacy Study of aQIV in Elderly Adults

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PROTOCOL SYNOPSIS V118_18 VERSION 5

Name of Sponsor:	**Protocol number:**	**Generic name of study vaccine(s):**
Seqirus UK Ltd.	V118_18	MF59-adjuvanted Quadrivalent Subunit Inactivated Egg-derived Influenza Vaccine Tetanus Toxoid, Reduced Diphtheria Toxoid and Acellular Pertussis Vaccine, Adsorbed

Title of Study:

A Phase III, Randomized, Observer-Blind, Controlled, Multicenter Clinical Study to Evaluate the Efficacy, Safety and Immunogenicity of an MF59-Adjuvanted Quadrivalent Influenza Vaccine Compared to Non-influenza Vaccine Comparator in Adults ≥ 65 Years of Age

Study Period:	**Clinical Phase:**
The total study period will be approximately 12 months following a single vaccination.	III

Background and Rationale:

The purpose of this study is to demonstrate the efficacy, safety and immunogenicity of an MF59-adjuvanted inactivated egg-derived quadrivalent influenza vaccine (aQIV) in preventing seasonal influenza in elderly adults. Seasonal influenza is a significant cause of morbidity and mortality, particularly in children and elderly (Neuzil, Mellen et al. 2000); (Mullooly, Bridges et al. 2007); (MMWR,2010). The efficacy of vaccination in preventing influenza in the elderly appears to be lower compared with younger adults (Osterholm, Kelley et al. 2012; Beyer, McElhaney et al. 2013). One potential explanation for the absolute decrease in vaccine efficacy compared with younger adults may be a less robust immune response after influenza vaccination (Goodwin, Viboud et al. 2006; Sasaki, Sullivan et al. 2011).

Therefore, novel approaches are sought to improve the immunogenicity of influenza vaccines in the elderly population. One way to increase immunogenicity of influenza vaccines is through the use of adjuvants, such as the squalene and water emulsion, MF59. FLUAD®, Seqirus' trivalent influenza vaccine combined with MF59, has been licensed for use in Europe since 1997. The administration of FLUAD® to elderly patients results in significantly higher geometric mean Haemagglutination Inhibition (HI) titers and rates of seroconversion in comparison to non-adjuvanted trivalent influenza vaccine (TIV) (Frey

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et al. 2014).

Most licensed influenza vaccines contain antigens derived from three strains of virus, A/H1N1, A/H3N2 and B. The B strains of virus are genetically classified into two main lineages, B/Yamagata and B/Victoria. During a typical influenza season, a single A/H1N1 and A/H3N2 will predominate. The epidemiology of disease caused by B strains is different and during the past decade it is common for both strains to circulate simultaneously (Ambrose and Levin et al. 2012). This can result in a clinically significant mismatch between the vaccine composition and circulating strains (Lo, Chuang et al. 2013). Quadrivalent vaccines contain HA and NA antigens from both B strains of influenza which may provide additional clinical benefit during seasons where a mismatch occurs.

Seqirus has recently begun the clinical study of aQIV in children, manufactured using a similar process to that of FLUAD®. The goal of this current randomized, observer-blind, controlled study is to demonstrate that aQIV prevents influenza in elderly adults. Direct comparison with a non-influenza comparator vaccine, Boostrix®, a tetanus toxoid, reduced diphtheria toxoid and acellular pertussis (TdaP) vaccine, licensed for use in elderly adults, will enable an estimation of the absolute efficacy of aQIV in preventing influenza in elderly adults while simultaneously providing benefit to subjects randomized to not receive influenza vaccine. Placebo or non-influenza vaccine comparators have been used to show influenza vaccine efficacy in elderly subjects (DeVilliers et al. 2009). This approach is consistent with CBER Guidance for the licensure of seasonal influenza vaccines and was recently used to demonstrate the benefit of an inactivated non-adjuvanted quadrivalent vaccine in children (Jain et al. 2013). The data from this study will be used to support the licensure of FLUAD® and aQIV for the prevention of seasonal influenza in adults ≥ 65 years of age.

Study Objectives:

The primary and secondary efficacy objectives will be measured in all subjects in relation to cases of influenza occurring from 21 through 180 days after vaccination or through the end of influenza season, whichever is longer. In all cases, efficacy will be determined

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based on influenza cases caused by A (H1N1 and H3N2) and either B lineage.

Primary Efficacy Objective:

1. To demonstrate absolute vaccine efficacy of aQIV versus non-influenza comparator (Boostrix®) when administered as a single dose to prevent first occurrence RT-PCR-confirmed influenza, due to any strain of influenza regardless of antigenic match to the strains selected for the seasonal vaccine, in subjects ≥ 65 years of age.

Primary Safety Objectives:

2. To evaluate the safety of aQIV through assessment for local and systemic solicited adverse events through Day 7 in a subset of subjects.
3. To evaluate the rates in each vaccine group of medically-attended adverse events within 30 days after the first occurrence RT-PCR confirmed ILI.
4. To evaluate the rates in each vaccine group of unsolicited adverse events for 21 days after vaccination and adverse events leading to withdrawal, serious adverse events (SAEs), adverse events of special interest (AESI), and new onset of chronic diseases (NOCD) for 365 days after vaccination.

Key Secondary Efficacy Objective:

1. To demonstrate absolute vaccine efficacy of aQIV versus non-influenza comparator when administered as a single dose to prevent first occurrence culture-confirmed influenza, due to strains antigenically matched to the strains selected for the seasonal vaccine.

Secondary Efficacy Objectives:

2. To evaluate absolute vaccine efficacy of aQIV versus non-influenza comparator when administered as a single dose to prevent first occurrence culture-confirmed influenza, due to any strain of influenza regardless of antigenic match to the strains selected for the seasonal vaccine.
3. To evaluate absolute vaccine efficacy of aQIV versus non-influenza comparator when administered as a single dose to prevent first occurrence culture-confirmed

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influenza, due to strains antigenically unmatched to the strains selected for the seasonal influenza vaccine.

4. To evaluate the absolute efficacy of aQIV versus non-influenza comparator when administered as a single dose to prevent first occurrence RT-PCR-confirmed influenza due to any strain of influenza regardless of antigenic match from 7 days to 180 days after vaccination or at the end of influenza season, whichever is longer (early efficacy).

Secondary Immunogenicity Objectives:

5. To evaluate the immunogenicity of aQIV measured by HI titer 21 days after vaccination, against influenza strains homologous to the seasonal vaccine.

Exploratory Immunogenicity Objective:

6. To characterize the immunogenicity of aQIV using other immunological assays (such as microneutralization assay).

7. To explore potential immune correlates of protection based on HI and/or other immunological assays (such as microneutralization assay).

   The results of this exploratory analysis may be presented in an addendum to the Clinical Study Report (CSR).

Study Design:

The study is a phase III, stratified, randomized, observer-blind, non-influenza comparator-controlled, multicenter study to evaluate the efficacy, safety and immunogenicity of an MF59-adjuvanted quadrivalent subunit influenza vaccine compared with a non-influenza comparator vaccine in subjects ≥ 65 years of age.

The study vaccine, aQIV, contains 15 µg of each of the four seasonal influenza strains (A/H1N1, A/H3N2, B [Yamagata and Victoria lineage]) and MF59 adjuvant. The non-influenza comparator (Boostrix®) vaccine will be used to provide a comparative

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assessment for efficacy, immunogenicity and safety.

Stratification according to age (≥ 65 to 74 and ≥ 75), study site and comorbidity status (at risk/ not at risk) will be performed (see Section 5.1.4, Randomization and Section 5.1.2, Screening). Sample size, among other factors, depends mainly on the number of RT-PCR confirmed influenza cases observed during the influenza seasons, so the overall number of subjects to be recruited provided here may change and enrolment over multiple seasons may be required to ensure 238 PCR-confirmed influenza cases have occurred and/or based on the results of the interim analysis for efficacy and futility. Nasopharyngeal swab samples will be analyzed in batches and the number of RT-PCR confirmed influenza cases will be reviewed on a regular basis. Once the number of RT-PCR confirmed influenza cases exceeds 119, an interim analysis for efficacy and futility with an appropriate adjustment of the type I error will be performed by an independent Data Monitoring Committee (DMC). Another interim analysis might be recommended before target 238 RT-PCR confirmed influenza cases are observed. Once the number of RT-PCR confirmed influenza cases is ≥ 238 the Sponsor will stop and unblind the trial and perform the final analysis. Stopping rules for futility and efficacy and any additional details regarding the DMC can be found in the DMC Charter.

Two definitions of ILI will be used. Primary protocol-defined ILI will be used to trigger nasopharyngeal swab retrieval and completion of the ILI booklet. The respiratory symptoms in both definitions are considered a new onset or exacerbation of a pre-existing condition.

- *Primary protocol-defined ILI*: At least one of the following respiratory symptoms: sore throat, cough, sputum production, wheezing, or difficulty breathing; concurrently with at least one of the following systemic symptoms: temperature of > 37.2°C/ 99°F, chills, tiredness, headache, or myalgia.
- *Modified Centers for Disease Control and Prevention (CDC) ILI definition*: Fever (temperature of > 37.2° C/99°F) with cough or sore throat.

The ILI onset day is defined as the first day that the subject meets the primary protocol-

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defined ILI.

Each subject will have two stages of study participation: Treatment Period (Day 1 to Day 22) and Follow-up Period (Day 23 to Day 366). A subset of subjects will be selected to participate in an assessment of immunogenicity and solicited adverse events.

The study procedures consist of four (4) clinic visits, and three (3) safety phone calls. After enrolment and vaccination on Day 1, all subjects will then return to the clinic for three (3) additional clinic visits, on Days 22, 181 and 366. During the study there will also be three (3) safety phone calls on Days 15, 91, and 271. Subjects participating in the solicited safety subset will receive an additional call on day 3 reminding them to complete their diary card.

Additionally, all subjects will receive weekly phone calls or messages to assess for primary protocol-defined ILI symptoms during the active ILI surveillance period, defined as from Day 1 through Day 181 or until the end of the influenza season, whichever is longer. The purpose of the ILI surveillance phone calls/message is to trigger a clinic or home visit to collect a nasopharyngeal swab. Subjects will also be asked for the duration of the trial (through day 366) to contact the site at the onset of ILI symptoms to schedule a clinic visit for NP swab collection.

After an initial screening, subjects will be vaccinated with a single dose of aQIV or non-influenza comparator on Day 1. Subjects will be observed for at least 30 minutes post-vaccination on Day 1 for any immediate reactions. Subjects participating in the solicited safety subset will receive a Subject Diary along with instructions to ensure proper completion and assessment on reactogenicity. These subjects will be instructed to complete a Subject Diary to describe solicited local and systemic adverse events that may occur post-vaccination from Day 1 through Day 7. For all subjects any adverse event and concomitant medication use, after vaccination from Day 1 to Day 22 will be collected at the Day 15 safety phone call and during the Day 22 clinic visit. Information collected at these visits will be documented in the subject's source records and captured in the Electronic Case Report Form (eCRF). All subjects will also receive an ILI booklet on Day 1, and will be instructed to measure their body temperature using the thermometer

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provided starting from onset day of primary protocol defined ILI to the day they come in to the clinic for the NP swab collection. Subjects will be asked to return the ILI booklet at the time of their NP clinic visit.

During the remaining follow-up phase of the study (up to Day 366), safety data including adverse events leading to withdrawal, AESI, NOCD, SAE and concomitant medication use related to these events will be captured via safety phone calls or clinic visits.

Subjects experiencing an ILI will have one (1) additional clinic visits and one (1) safety call: (1) a clinic or home visit to collect a nasopharyngeal (NP) swab as soon as possible preferably within 3, but up to 6, days after the first day of onset of primary protocol-defined ILI symptoms, and (2) a safety follow-up call 30 days after ILI onset to determine if subsequent medically-attended adverse events occurred and concomitant medication associated with these events were used. The use of anti-viral medications will be permitted after a NP swab has been obtained and will be documented as concomitant medications. Nasopharyngeal swabs will be processed for viral culture and RT-PCR confirmation. Culture positive samples will undergo antigenic characterization.

One season in which at least 2800 subjects are anticipated to be enrolled will be selected for the collection of immunogenicity samples. Samples from approximately 2800 subjects participating in the selected season will be collected at Day 1 (baseline) and Day 22 (visit 3). In order to maintain the study blind equal numbers of subjects from both treatment groups will be asked to provide blood specimens (see Section 3.5, Collection of Clinical Specimens). After all of the specimens have been obtained a subset of samples from those collected will be randomly selected on a 4:1 ratio (1,362 aQIV; 340 Boostrix) for the purpose of completing the analysis of the immunogenicity objectives. Anti-HA antibody will be measured using a validated haemagglutination inhibition (HI) assay with egg-derived HA antigens from homologous strains of the virus. Serum samples from subjects with RT-PCR confirmed influenza, along with a subset of subjects who did not have RT-PCR confirmed influenza, may be tested to estimate the correlate of protection. The serologic component of the correlate of protection will be measured using either a validated haemagglutination inhibition (HI) and/or other immunological assays (such as

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microneutralization).		

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Number of Subjects Planned:

As described in the study design section this study will employ group sequential design and therefore the total study size (and study duration) will depend on the number of RT-PCR confirmed influenza cases observed during the influenza seasons (see Section 3.7, DMC and Section 8.6, Interim Analysis).

The sample size, among other factors, depends mainly on the number of PCR-confirmed influenza cases observed during the influenza seasons so the overall number of subjects to be recruited may change and enrolment over multiple seasons may be required to ensure 238 PCR-confirmed influenza cases have occurred and/or based on the results of the interim analysis for efficacy and futility. It is anticipated that in order to obtain 238 cases, including a drop-out rate of 10%, approximately 10,692 subjects ≥ 65 years, will need to be enrolled into the trial. Approximately 5,346 subjects will be enrolled per vaccine group will be randomized to receive either aQIV or non-influenza comparator (Boostrix®) in a 1:1 allocation ratio, stratifying by age (≥ 65 to 74 and ≥ 75) and by comorbidity status (at risk/not at risk, see Section 5.1.2, Screening).

Specimens from those collected during the immunogenicity season will be randomly selected in a 4:1 ratio for analysis. In total approximately 1,702 of the up to 2800 samples collected are planned to be included the analysis (1,362 aQIV; 340 Boostrix). The serum samples may also be analyzed to facilitate the estimation of immune correlate of protection.

With 4,860 evaluable subjects in each treatment group, the probability of detecting a rare safety event which occurs at 0.001 (1/1000) rate will be 99%. Approximately 2,100 subjects are planned to be enrolled in the Solicited Safety Subset. With 1,053 subjects in each treatment group, the probability of detecting a rare safety event which occurs at 0.002 (1/500) rate will be ≥86%, assuming a drop-out/missing data rate of up to 5%. The number of enrolled subjects should be sufficient to capture such adverse events.

More details on sample size calculation can be found in the respective section on sample size and power considerations of this synopsis.

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Study Population and Subject Characteristics:

This study will enroll males and females ≥ 65 years old who are healthy or are at risk of complications from influenza infection.

The list of inclusion and exclusion criteria is included in protocol Section 4, Selection of Study Population.

Study Procedures:

All subjects enroled in this study will receive a single vaccination with either aQIV or non-influenza comparator (Boostrix®). For the full course of the trial (Day 1-366) subjects will be asked to notify study personnel at the onset of ILI symptoms, (preferably within 3, but up to 6, days), so that either unscheduled clinic evaluation or home visit to retrieve nasopharyngeal (NP) swab samples, can be occur. All subjects will also receive an ILI booklet on Day 1, and will be instructed to measure their body temperature using the thermometer provided starting from onset day of primary protocol defined ILI to the day they come in to the clinic for their NP swab collection. Subjects will be asked to return the ILI booklet at the time of their NP clinic visit.

During the Treatment Period on Day 15, for all subjects a safety phone call will be performed to collect information regarding unsolicited adverse events and concomitant medication. On Day 22 a symptom directed physical examination will be performed by a qualified health care practitioner in addition to evaluating safety data on all subjects. During the Follow-up Period subjects will be asked to return to the clinic for two (2) additional scheduled visits for a symptom directed physical examination and to evaluate safety on Day 181 and Day 366. Additionally, all subjects will participate in two (2) safety phone calls on Days 91, and 271. Subjects will also receive weekly phone calls or messages to assess for ILI symptoms during the active ILI surveillance period, defined as Day 1 through Day 181 or until the end of the influenza season whichever is longer.

Subjects experiencing a primary protocol-defined ILI will have one (1) additional clinic visit and one (1) additional safety call which will be scheduled relative to the timing of the ILI: (1) a clinic or home visit to collect a nasopharyngeal swab as soon as possible

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following the onset of symptoms (preferably within 3, but up to 6, days after the first day of ILI symptoms). Subjects with a NP swab taken for an ILI will be contacted by phone for a safety follow-up call 30 days after ILI onset to capture all medically-attended adverse events, and concomitant medication use.

Subjects participating in the immunogenicity subset will have blood samples collected at their clinic visits 1 and 3 (Days 1 and 22). Subjects participating in the solicited safety subset will be asked to return their completed Subject Diary at their Day 22 clinic visit.

If a subject withdraws from the study, they will be asked to undergo a final assessment for safety.

Study Vaccines:

The study vaccine is an egg-derived quadrivalent inactivated subunit influenza vaccine which includes MF59 adjuvant. Haemagglutinin and neuraminidase antigens are derived from the four influenza virus strains (A/H1N1, A/H3N2, B/Yamagata and Victoria lineage) recommended by the US CDC and WHO (World Health Organization) for inclusion in the seasonal vaccine. Fifteen (15) µg of each HA antigen is present in 0.5 ml of the vaccine which is formulated in a pre-filled syringe (PFS).

The non-influenza comparator, TdaP, is a non-infectious, sterile, vaccine indicated for active booster vaccination against tetanus, diphtheria and acellular pertussis. It contains tetanus toxoid, reduced diphtheria toxoid, and pertussis antigens (inactivated pertussis toxin [PT] and formaldehyde-treated filamentous haemagglutinin [FHA] and pertactin).

Efficacy Endpoints:

The primary efficacy endpoint is the time of first-occurrence of RT-PCR-confirmed influenza due to A (H1N1 and H3N2) or either B lineage due to any strain of influenza regardless of antigenic match to the strains selected for the seasonal vaccine from 21 through 180 days after vaccination or end of the influenza season, whichever is longer.

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The end of the influenza season will be defined as the end of June for Northern Hemisphere (NH) influenza season and end of December for Southern Hemisphere (SH) influenza season. For tropical countries, with no typical NH or SH influenza season, the season is defined by the use of the strains in the vaccine formulation (i.e. strains as recommended for the NH or the SH influenza season) and the timing of vaccination. The investigators will be advised of the date enrollment will be closed in their country or hemisphere. The actual date selected for the end of each season in each hemisphere will be documented in the SAP.

In addition to the primary efficacy endpoint, additional endpoints for the secondary efficacy objectives are sought, based on antigenic match of culture isolated influenza to the strains of virus contained in the seasonal vaccine.

Vaccine efficacy will be determined based on either:

- Antigenically matched strains of influenza virus (Secondary Efficacy Objective 1)
- Influenza strains regardless of antigenic match (Secondary Efficacy Objectives 2 and 4)
- Antigenically unmatched strains of influenza virus (Secondary Efficacy Objective 3)

An influenza event is defined as RT-PCR or culture-confirmed influenza infection in the setting of an influenza-like illness (ILI). Two definitions of ILI will be used in this study. Primary protocol-defined ILI requires at least one of the following respiratory symptoms: sore throat, cough, sputum production, wheezing, or difficulty breathing; concurrently with at least one of the following systemic symptoms: temperature of > 37.2°C/ 99°F, chills, tiredness, headache, or myalgia and is based on that used to demonstrate the efficacy of Fluzone High Dose (DiazGranados, 2014). The second (modified CDC) definition will be fever (temperature of > 37.2°C/ 99°F) with cough or sore throat. The respiratory symptoms in both definitions are considered a new onset or exacerbation of a pre-existing condition. The primary and key secondary efficacy endpoints will be assessed using the primary protocol-defined ILI definition to determine success in the study. Primary and secondary efficacy objectives 1-4 will also be analyzed using both

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definitions of the first occurrence of ILI.

Subgroup analyses based on age-related cohorts (≥65-74, ≥75-84, and ≥85 years), baseline risk of complications from ILI and other demographic factors including baseline medical comorbidity and current smoking status will be performed for primary and all secondary endpoints.

Safety Endpoint(s):

- Safety objective 2 will be assessed by calculating the percentage of subjects in the solicited safety subset with solicited local and systemic adverse events from Day 1 through Day 7. Solicited local and systemic adverse event data from Day1-7 will be obtained from data collected on the subject diaries. Only subjects randomly selected for participation in the solicited safety subset will be asked to fill out a Subject Diary from Day 1-7.

Safety objectives will be assessed by comparing the following between cohorts that received aQIV or non-influenza comparator:

- Percentage of subjects with medically-attended adverse events within 30 days after the first occurrence ILI.
- Percentage of subjects with any unsolicited AEs and concomitant medications reported from Day 1 through Day 22.
- Percentage of subjects reporting SAEs, AEs leading to withdrawal from the study, NOCD, AESI and all concomitant medications associated with these events from Day 1 to Day 366.

Immunogenicity Endpoint(s):

The measures of immunogenicity used for Objective 5 as determined by the HI assay against homologous strains at Days 1 and 22, include the following:

- Geometric mean HI titer (GMT).

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- Geometric mean ratio calculated at Day 22/Day 1.
- Percentage of subjects with an HI titer ≥1:40.[1]
- Percentage of subjects achieving seroconversion (defined as: HI titer ≥1:40 for subjects sero-negative at baseline [HI titer <1:10]; or a minimum 4-fold increase in HI titer for subjects sero-positive at baseline [HI titer ≥1:10]) on Day 22.[1]
- Reverse cumulative distributions of HI titers at Day 22.

Exploratory Endpoint(s):

The exploratory endpoints determined by the microneutralization (MN) assay against homologous strains at Days 1 and 22, include the following:

- Geometric mean titer (GMT).
- Geometric mean ratio calculated at Day 22/Day 1.
- Percentage of subjects with a four-fold rise in MN antibody titer at Day 22
- Reverse cumulative distributions of MN titers at Day 22.

Additionally, an estimate of the serologic correlate of protection on the basis of HI or other immunological responses including MN, measured three weeks after vaccination against the respective strain

[1] The endpoints based on percent of subjects achieving seroconversion and HI titer ≥ 1:40 at Day 22 will be assessed against the criteria described in CBER Guidance Clinical Data Needed to Support the Licensure of Seasonal Inactivated Influenza Vaccines (2007). Specifically, this will be that:

- The lower bound of the two-sided 95% CI for the percent of subjects achieving seroconversion for HI antibody should meet or exceed 30%
- The lower bound of the two-sided 95% CI for the percent of subjects achieving an HI antibody titer ≥ 1:40 should meet or exceed 60%

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Statistical Analyses:

Criteria for Assessing Primary Efficacy Objective:

Primary Efficacy Objective:

The primary measure of absolute efficacy will be tested in elderly subjects ≥ 65 years of age according to the following null (H_0) and alternative (H_1) hypotheses:

$$H_0: 1- HR = VE \leq 0.4 \qquad \text{versus} \qquad H_1: VE > 0.4$$

where HR is defined as hazard ratio of the incidence of protocol defined ILI in aQIV versus a non-influenza comparator that will be estimated by the proportional hazards model. More details on the analysis methods will be described in the Statistical Analysis Plan (SAP).

The study is successful if the lower-limit (LL) of the two-sided 95% confidence interval (CI) (to be adjusted for one interim analysis) of absolute vaccine efficacy endpoint > 0.4. In case another interim analysis is necessary the type 1 error alpha and hence the CI will be adjusted.

Overall Study Success Criteria:

The study is successful if the primary efficacy objective is achieved.

Sample Size and Power Calculation for Primary Objective:

Sample size and power consideration for the aQIV efficacy objective is based on criteria for demonstrating efficacy in placebo controlled studies provided in CBER guidance, specifically that the study should be powered to assess the lower bound of the two-sided 95% CI of vaccine effectiveness, anticipated to be substantially above zero.

This study is planned using a group sequential design. The power of Cox Regression which is planned to be used for analysis is dependent on the overall number of RT-PCR

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confirmed influenza cases, so the sample sizes on number of subjects described in the sections above is provided more for operational reasons. Additional information is described in Section 8.6, Interim Analysis.

For the primary efficacy objective: with 1-sided alpha of 2.5% (adjusted for possible interim analysis) and assuming an attack rate of influenza of 3.5% among subjects enroled in the non-influenza comparator group and 1.4% among the aQIV group, i.e. 60% assumed vaccine efficacy for aQIV, 238 events (i.e. 5,346 subjects per group under the assumed event rates (ER)) are needed with 86.5% power to show the absolute efficacy of aQIV versus non-influenza comparator, in preventing first occurrence RT-PCR confirmed influenza A and/or B, due to any strain of influenza regardless of antigenic match to the strains in aQIV, in subjects ≥ 65 years of age, using a margin of 40% for lower bound of the CI for absolute vaccine efficacy[2].

For the first secondary efficacy objective: With group vaccine efficacy of 65% but expecting conservatively reduced ERs of RT-PCR confirmed influenza cases due to matched strains of 2.5% among subjects in the non-influenza comparator group and 0.9% among the aQIV group then 144 events are estimated with power approximately 88.5% to show the absolute efficacy of aQIV versus non-influenza comparator, using a margin of 40% for lower bound of the 95% CI.

Assuming a drop-out rate of 10%, approximately 10,692 subjects ≥ 65 years, 5,346 per vaccine group will be randomized to receive either aQIV or non-influenza comparator (Boostrix®) in a 1:1 allocation ratio, stratifying by age groups:

≥ 65 to 74 and ≥ 75 years of age and by the presence or absence of medical co- morbidity (see Section 5.1.2, Screening for assessment of comorbidity and risk of complications

[2] The attack rate of 3.5% is estimated based on the attack rate published in placebo controlled studies (DeVilliers, 2009; Treanor, 2011; Frey, 2009)

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from influenza).

Sample Size for Secondary Immunogenicity Objective (Immunogenicity Subset):

The immunogenicity objective is considered as secondary and so no alpha adjustment for multiplicity will be done for the analysis therefore a significance level of 5% (2-sided) or 2.5% (1-sided) was used for sample size calculation.

Using the following assumptions from the V70_27 study in elderly adult subjects: specifically after aTIV vaccination, seroconversion rates, H1N1: 77%, H3N2: 74% and B: 47%, and percentages of subjects with a HI titer ≥ 40, H1N1: 91%, H3N2: 99%, B: 64% (Table 1).

With samples analyzed from 1,362 subjects (1,226 evaluable subjects assuming a rate of 10% for missing data) in the aQIV group there will be at least 80% power to evaluate CBER criteria with all four strains contained in aQIV.

Table 1: CBER criteria for subjects ≥ 65 years of age

Strain	π_i (proportion in aQIV, based on data of V70_27)	π_0 (CBER threshold)	Sample size for aQIV	Marginal Power
Proportion of subjects with Seroconversion				
H1N1	77%	30%	1226	99%
H3N2	74%	30%	1226	99%
B strains	47%	30%	1226	99%
Proportion of subjects with HI titer ≥40				
H1N1	91%	60%	1226	99%
H3N2	99%	60%	1226	99%
B strains	64%	60%	1226	82%

Name of Sponsor: Seqirus UK Ltd.	**Protocol number:** V118_18	**Generic name of study vaccine(s):** MF59-adjuvanted Quadrivalent Subunit Inactivated Egg-derived Influenza Vaccine Tetanus Toxoid, Reduced Diphtheria Toxoid and Acellular Pertussis Vaccine, Adsorbed

Sample Size for Safety:

With 4,860 evaluable subjects in each treatment group, the probability of detecting a rare safety event which occurs at 0.001 (1/1000) rate will be 99%. With 1,053 subject selected for Solicited Safety Subset, assuming up to 5% dropout/missing data rate; there will at least 1000 evaluable subjects for analysis of solicited adverse events. With 1000 evaluable subjects in each treatment group, the probability of detecting a safety event which occurs at a rate of 0.002 will be 86%.

Interim Analysis:

Unblinded interim analyses for efficacy and futility will be performed by an independent DMC if the number of RT-PCR confirmed influenza cases observed ranges between 119 and 238. After formally requesting unblinding, the DMC will be provided with the unblinded data generated by an unblinded statistician to enable unblinded analysis of the interim dataset during a closed session. Another interim analysis might be recommended before target 238 cases are observed.

Further details regarding the interim analysis are given in Section 8.6, Interim Analysis.

Name of Sponsor: Seqirus UK Ltd.	**Protocol number:** V118_18	**Generic name of study vaccine(s):** MF59-adjuvanted Quadrivalent Subunit Inactivated Egg-derived Influenza Vaccine Tetanus Toxoid, Reduced Diphtheria Toxoid and Acellular Pertussis Vaccine, Adsorbed

Data Monitoring Committee:

An independent DMC will be used for this study. The main purpose of the DMC will be to ensure the safety of subjects and scientific integrity of the study on an ongoing basis during the trial. The DMC will review blinded, and if requested, semi- or fully -unblinded safety and efficacy data during the study. The DMC will perform the interim analysis for futility and efficacy and make a recommendation about continuing or stopping the trial. Unblinded data will be reviewed in closed sessions of the DMC, without participation of the Sponsor. All descriptions of these closed sessions will be unavailable to the Sponsor until study unblinding has occurred.

After reviewing safety and efficacy data, the DMC will recommend that enrolment be continued, halted temporarily (pending additional information from the Sponsor or modification to the study design) or halted permanently as specified in the Charter. Stopping rules for futility and efficacy and any additional details regarding the DMC can be found in the DMC Charter and in Section 3.7, Data Monitoring Committee of the protocol.

Table 2: Time and Events Table – Treatment Period

	Visit Type	Clinic Visit	Reminder Phone Call[b]	Safety Phone Call	Clinic Visit
	Study Day	**1**	**3**	**15**	**22**
	Visit Window (Days)	**N/A**	**+/- 1**	**+/- 3**	**-1 to +4**
	Visit Number	**1**		**2**	**3**
Study Event	**References**				
Study Treatment					
Vaccination	Section 5.2	X			
Screening and Safety					
Informed Consent [a]	Section 5.1.1	X [f]			
Medical History	Sections 5.1.2	X [f]			
Physical Exam	Sections 5.1.2 and 5.3.1	X [c, f]			X
Exclusion/Inclusion Criteria	Section 4.0	X [f]			
Randomization	Section 5.1.4	X [f]			
30 Minutes Post Injection Assessment	Section 5.2.1	X			
Subject Diary Dispensed with Training[b]	Section 5.2.1	X			
Subject Diary Reminder Call[b]	Section 5.2.2		X		
Subject Diary Reviewed and Collected[b]	Section 5.3.1				X
Assess all AEs	Sections 7.1.1 and 7.1.3	X		X	X
Assess SAEs	Section 7.1.4	X		X	X

	Visit Type	Clinic Visit	Reminder Phone Call[b]	Safety Phone Call	Clinic Visit
	Study Day	1	3	15	22
	Visit Window (Days)	N/A	+/- 1	+/- 3	-1 to +4
	Visit Number	1		2	3
Study Event	**References**				
Assess for NOCDs, AEs leading to withdrawal, ILI and AESIs	Sections 7.1.4.1 and 7.1.3	X		X	X
Assess Relevant Medications/ Vaccinations	Sections 5.1.2 and 6.5	X		X	X
Efficacy					
ILI Instruction Sheet Dispensed	Section 5.2.1	X			
ILI Booklet Dispensed with Instructions	Section 5.2.1	X			
Message/ Phone Call to Assess ILI	Section 5.3.3	X[d]			
Immunogenicity					
Serology Blood Draw[e]	Section 3.5	X[f]			X

Notes:

[a] Confirm consent form(s) signed prior to any procedures. The informed consent process may be conducted earlier, but within 10 days prior to Day 1.

[b] Only applies to subjects who have been selected for participation in the solicited safety subset.

[c] Includes measurement of height and weight.

[d] Message/ phone call surveillance for primary protocol-defined ILI to be performed on a weekly basis from Study Day 1 through Study Day 181 or end of the influenza season, whichever is longer.

[e] Only applies to subjects selected for participation in the immunogenicity subset

[f] Procedures to be performed prior to vaccination.

Table 3: Time and Events Table – Follow-up Period

	Visit Type	Safety Phone Call	Clinic Visit	Safety Phone Call	Clinic Visit
	Study Day	**91**	**181**	**271**	**366**
	Visit Window (Days)	**+/- 3**	**+/- 7**	**+/- 3**	**-60 to +30**
	Visit Number	**4**	**5**	**6**	**7**
Study Event	**References**				
Safety					
Physical Exam	Sections 5.1.2 and 5.3.1		X		X
Assess SAEs	Section 7.1.4	X	X	X	X
Assess for NOCDs, AEs leading to withdrawal, ILI and AESIs	Sections 7.1.4.1 and 7.1.3	X	X	X	X
Assess Relevant Medications/ Vaccinations	Sections 5.1.2 and 6.5	X	X	X	X
Efficacy					
Message/ Phone Call to Assess ILI	Section 5.3.3	X[a]			
Study Completion Procedures					
Study Termination [b]	Section 5.5				X

Notes:

[a] Message/ phone call surveillance for primary protocol-defined ILI to be performed on a weekly basis from Study Day 1 through Study Day 181 or end of the influenza season, whichever is longer.

[b] Subjects who terminate the study early are recommended to complete certain study-related procedures. See section 5.5, Study Termination Visit for further details.

Table 4: Time and Events Table – ILI Visit Schedule

	Visit Type	Clinic Visit[a]	ILI Follow-up Safety Call
	ILI Day	1-4	30
	Visit Window (Days)	+3	+7
	Visit Number	n/a	n/a
Study Event	**References**		
NP Swab Specimen Collection	Section 5.4	X	
Assess ILI symptoms and Relevant Medications	Section 5.4	X	X
Assess for Medically-Attended Adverse Events	Section 5.4	X	X
Assess Relevant Medications	Section 5.4	X	
Physical Exam	Section 5.4	X	
ILI Booklet Reviewed and Collected	Section 5.4	X	

Notes:
[a] The Clinic Visit should occur as soon as possible within 3 days after the first day of onset of ILI symptoms (Day 1-4), but up to 6 days.

LIST OF ABBREVIATIONS

ACIP	Advisory Committee on Immunization Practices
AE	Adverse Event
AESI	Adverse Events of Special Interest
BLA	Biologics Licensure Application
B&SR	Biostatistics and Statistical Reporting
BMI	Body Mass Index
CBER	Center for Biologics Evaluation and Research
CDC	Centers for Disease Control and Prevention
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence Interval
CRF	Case Report Form
CRO	Contract Research Organization
CSR	Clinical Study Report
DCF	Data Clarification Form
DMC	Data Monitoring Committee
EC	Ethics Committee
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
EMA	European Medicines Agency
ER	Event Rate
FAS	Full Analysis Set
FDA	United States Food and Drug Administration
GCP	Good Clinical Practices
GMC	Geometric Mean Concentration
GMR	Geometric Mean Ratio
GMT	Geometric Mean Titer
HA	Haemagglutinin
HI	Haemagglutination Inhibition
HIPAA	Health Insurance Portability and Accountability Act
HIV	Human Immunodeficiency Virus
IB	Investigator's Brochure
ID	Identification
ICF	Informed Consent Form
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
ILI	Influenza-Like Illness
IM	Intramuscular
IRB	Institutional Review Board
IRT	Interactive Response Technology

MedDRA	Medical Dictionary for Regulatory Activities
MN	Microneutralization
NA	Neuraminidase
NOCD	New Onset of Chronic Disease
NP	Nasopharyngeal
NH	Northern Hemisphere
PCR	Polymerase Chain Reaction
PFS	Pre-filled Syringes
PP	Per Protocol
PPS	Per Protocol Set
PRO	Patient Reported Outcome
PV	Pharmacovigilance
PT	Pertussis Toxin
aQIV	Adjuvanted Quadrivalent Influenza Vaccine
QIV	Quadrivalent Influenza Vaccine
RT-PCR	Reverse Transcription Polymerase Chain Reaction
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SC	Seroconversion
SDA	Source Data Agreement
SOC	System Organ Class
SOP	Standard Operating Procedure
TdaP	Tetanus Toxoid, Reduced Diphtheria Toxoid and Acellular Pertussis
TIV	Trivalent Influenza Vaccine
TNF	Tumor Necrosis Factor
VSAE	Vaccine Serious Adverse Events
WHO	World Health Organization

DEFINITIONS

Culture confirmed matched strains are defined by as those with a < 8 fold difference in titer as compared to the vaccine strain.

Culture confirmed unmatched strains are defined as those with a ≥ 8 fold difference in titer as compared to the vaccine strain.

End of influenza season: The end of the influenza season will be defined as the end of June for Northern Hemisphere (NH) influenza season and end of December for Southern Hemisphere (SH) influenza season. For tropical countries, with no typical NH or SH influenza season, the season is defined by the use of the strains in the vaccine formulation (i.e. strains as recommended for the NH or the SH influenza season) and the timing of vaccination.

Influenza case: An ILI associated with RT-PCR or culture confirmed influenza.

ILI onset: The first day on which a subject fulfils the criteria for protocol-defined ILI.

Medically-attended Adverse Event[3]: Defined as symptoms or illnesses requiring hospitalization, or emergency room visit, or visit to/by a health care provider.

Modified CDC Influenza-like illness (ILI)[4]: Fever (temperature of > 37.2°C/ 99°F) with cough or sore throat.

Protocol-defined ILI: At least one of the following respiratory symptoms: sore throat, cough, sputum production, wheezing, or difficulty breathing; concurrently with at least one of the following systemic symptoms: temperature of > 37.2°C/ 99°F, chills, tiredness, headache, or myalgia.

Qualified healthcare professional: Any licensed health care professional who is permitted by institutional policy to perform clinical interventions and assessments such as physical examinations and who is identified within the Study Staff Signature Log.

Trained healthcare professional: Any health care professional who is permitted by institutional policy and trained to perform delegated tasks and who is identified within the Study Staff Signature Log.

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[3] Please also refer to the CRF instructions for further guidance.

[4] The respiratory symptoms in both definitions are considered a new onset or exacerbation of a pre-existing condition.

1. BACKGROUND AND RATIONALE

1.1 Background

Seasonal influenza is a major cause of morbidity and mortality in the elderly. On average from 1976 through 2007, nearly 90% of all deaths attributed to seasonal influenza in the United States occurred in people 65 years of age or older. During this period the number of deaths per year in the elderly population ranged from 673 to 5,546 per year (MMWR, 2010). Much of the mortality attributed to influenza is due to respiratory and cardiovascular illnesses, such as secondary bacterial pneumonia and exacerbation of underlying cardiac and respiratory disease (Mullooly, 2007).

Vaccination is an effective way to prevent influenza and the related complications. In the US seasonal influenza vaccination was estimated to prevent 3.2 million medically attended illnesses and nearly 80,000 fewer hospitalizations (MMWR, 2013). It is estimated that 56% of the prevented hospitalizations were amongst patients 65 year or older (MMWR, 2013). In an earlier study of elderly not residing in chronic care facilities, vaccination was associated with a 27% reduction in the risk of hospitalization for pneumonia or influenza and a 48% reduction in the risk of death (Nichol, 2007). Seasonal influenza vaccination also appears to have a salutary effect on the incidence of cardiac diseases. In a prospective randomized controlled study of patients with recent myocardial infarction, seasonal influenza vaccination reduced the incidence of subsequent cardiovascular death and re-hospitalization (Gurfinkel, 2002). Since the majority of influenza-related hospitalizations and deaths occur in the elderly, the derived benefit of vaccination in this age group is large. However, the effectiveness and efficacy of current influenza vaccines is substantially reduced in the elderly relative to younger populations (Osterholm, 2012; Beyer, 2013 and MMWR 2013). The reason for the reduced efficacy of influenza vaccines in the elderly is not completely known but may be explained by qualitative and quantitative differences in the immune response after vaccination (Goodwin, 2006; Sasaki 2011). The risk of complications from influenza infection is uniform amongst the elderly and chronic medical illness appears to increase the risk of hospitalization due to pneumonia and influenza and death. A clinical prediction rule was previously developed and validated to determine the risk of complications from influenza infection in the elderly (Hak, 2004).

Therefore, vaccines with improved effectiveness in the elderly could further reduce the burden of disease resulting from complications of influenza. One way to increase immunogenicity of influenza vaccines is through the use of adjuvants, such as the squalene and water emulsion, MF59. FLUAD®, Seqirus' trivalent influenza vaccine combined with MF59, has been licensed for use in Europe since 1997. When administered to elderly, this vaccine results in significantly higher geometric mean HI titers and rates of seroconversion in comparison to a non-adjuvanted trivalent influenza

vaccine (TIV) (Scheifele, 2013; Frey et al. 2014). The improved immunogenicity of FLUAD is not associated with significant increase in risk compared with non-adjuvanted vaccine. Administration of FLUAD to elderly patients results in higher local and systemic reactogenicity compared with non-adjuvanted vaccines but the reactions are mild and self-limited (Scheifele, 2013; Frey, 2014). In a large prospective, observational study and a smaller, retrospective, case-control study, FLUAD appears to be more effective than non-adjuvanted comparators (Mannino, 2012; VanBuynder, 2013). Furthermore, there does not appear to be an increased risk of rare but potentially serious adverse events based on a prospective analysis of subjects enroled in the study referred to above (Villa, 2013).

Seqirus has received accelerated approval by the United States Food and Drug Administration (FDA) to market FLUAD for the prevention of seasonal influenza in elderly subjects. Final licensure through the accelerated approval pathway is dependent on the demonstration of clinical benefit. Seqirus proposes to use a quadrivalent inactivated influenza vaccine combined with the adjuvant MF59, in this study and the FDA has agreed with this approach. Both aTIV and aQIV subunit vaccines are manufactured in a similar way and, in the case of aQIV, the fourth antigen is derived from a second B strain of influenza. B strains of influenza viruses are genetically classified into two main lineages, B/Yamagata and B/Victoria. During a typical influenza season, a single A/H1N1 and A/H3N2 will predominate. The epidemiology of disease caused by B strains is different and during the past decade it is common for both strains to circulate simultaneously (Ambrose and Levin et al. 2012). This can result in a clinically significant mismatch between the vaccine composition and circulating strains (Lo, Chuang et al. 2013).

The goal of this current randomized, observer-blind, controlled study is to demonstrate that aQIV prevents influenza in elderly adults. Direct comparison with a non-influenza comparator vaccine (Boostrix®) licensed for use in elderly adults, will enable an estimation of the absolute efficacy of aQIV in preventing influenza in elderly adults while simultaneously providing benefit to subjects randomized to not receive influenza vaccine. Placebos, or non-influenza vaccine comparators, have been used to show influenza vaccine efficacy in elderly subjects (DeVilliers et al. 2009). This approach is consistent with CBER Guidance for the licensure of seasonal influenza vaccines and was recently used to demonstrate the benefit of an inactivated non-adjuvanted quadrivalent vaccine in children (Jain et al. 2013).

The data from this study will be used to support the licensure of FLUAD and aQIV for the prevention of seasonal influenza in adults 65 years of age and older.

1.2 Rationale

The purpose of this study is to demonstrate the clinical efficacy of Seqirus' adjuvanted inactivated quadrivalent vaccine in adults 65 years of age and older. This randomized, observer-blind, non-influenza comparator-controlled study is intended to demonstrate that aQIV prevents RT-PCR confirmed influenza. This study is intended to fulfil a requirement of the accelerated approval pathway in the US. In particular to demonstrate the clinical benefit of aQIV, the quadrivalent version of Fluad, which was recently licensed for use in the US in adults 65 years and older.

2. OBJECTIVES

2.1 Primary Objective(s)

The primary and secondary efficacy objectives will be measured in all subjects in relation to cases of influenza occurring from 21 through 180 days after vaccination or through the end of influenza season, whichever is longer. In all cases, efficacy will be determined based on influenza cases caused by A (H1N1 and H3N2) and either B lineage.

Primary Efficacy Objective:

1. To demonstrate absolute vaccine efficacy of aQIV versus non-influenza comparator (Boostrix®) when administered as a single dose to prevent first occurrence RT-PCR-confirmed influenza, due to any strain of influenza regardless of antigenic match to the strains selected for the seasonal vaccine, in subjects ≥ 65 years of age.

Primary Safety Objectives:

2. To evaluate the safety of aQIV through assessment for local and systemic solicited adverse events through Day 7 in a subset of subjects.
3. To evaluate the rates in each vaccine group of medically-attended adverse events within 30 days after the first occurrence RT-PCR confirmed ILI.
4. To evaluate the rates in each vaccine group of unsolicited adverse events for 21 days after vaccination and adverse events leading to withdrawal, serious adverse events (SAEs), adverse events of special interest (AESI), and new onset of chronic diseases (NOCD) for 365 days after vaccination.

2.2 Secondary Objective(s)

Key Secondary Efficacy Objective:

1. To demonstrate absolute vaccine efficacy of aQIV versus non-influenza comparator when administered as a single dose to prevent first occurrence culture-confirmed influenza, due to strains antigenically matched to the strains selected for the seasonal vaccine.

Secondary Efficacy Objectives:

2. To evaluate absolute vaccine efficacy of aQIV versus non-influenza comparator when administered as a single dose to prevent first occurrence culture-confirmed influenza, due to any strain of influenza regardless of antigenic match to the strains selected for the seasonal vaccine.

3. To evaluate absolute vaccine efficacy of aQIV versus non-influenza comparator when administered as a single dose to prevent first occurrence culture-confirmed influenza, due to strains antigenically unmatched to the strains selected for the seasonal influenza vaccine.
4. To evaluate the absolute efficacy of aQIV versus non-influenza comparator when administered as a single dose to prevent first occurrence RT-PCR-confirmed influenza due to any strain of influenza regardless of antigenic match from 7 days to 180 days after vaccination or at the end of influenza season, whichever is longer (early efficacy).

Secondary Immunogenicity Objective:

5. To evaluate the immunogenicity of aQIV measured by HI titer 21 days after vaccination, against influenza strains homologous to the seasonal vaccine.

2.3 Exploratory Objective(s)

1. To characterize the immunogenicity of aQIV using other immunological assays (such as microneutralization assay).

2. To explore potential immune correlates of protection based on HI and/or other immunological assays (such as microneutralization assay).

3. STUDY DESIGN

3.1 Overview of Study Design

The study is a phase III, stratified, randomized, observer-blind, non-influenza comparator-controlled, multicenter study to evaluate the efficacy, safety and immunogenicity of an MF59-adjuvanted quadrivalent subunit influenza vaccine compared with a non-influenza comparator vaccine in subjects ≥ 65 years of age.

The study vaccine, aQIV, contains 15 µg of each of the four seasonal influenza strains (A/H1N1, A/H3N2, B [Yamagata and Victoria lineage]) and MF59 adjuvant. The non-influenza comparator (Boostrix®) vaccine will be used to provide a comparative assessment for efficacy, immunogenicity and safety.

Stratification according to age (≥ 65 to 74 and ≥ 75 years), study site and comorbidity status (at risk/not at risk) will be performed (see Section 5.1.4, Randomization and Section 5.1.2, Screening). Sample size, among other factors, depends mainly on the number of RT-PCR confirmed influenza cases observed during the influenza seasons, so the overall number of subjects to be recruited provided here may change and enrolment over multiple seasons may be required to ensure 238 PCR-confirmed influenza cases have occurred and/or based on the results of the interim analysis for efficacy and futility. Nasopharyngeal swab samples will be analyzed in batches and the number of RT-PCR confirmed influenza cases will be reviewed on a regular basis. Once the number of RT-PCR confirmed influenza cases exceeds 119, an interim analysis for efficacy and futility with an appropriate adjustment of the type I error will be performed by an independent Data Monitoring Committee (DMC). Another interim analysis might be recommended before target 238 RT-PCR confirmed influenza cases are observed. Once the number of RT-PCR confirmed influenza cases is ≥ 238 the Sponsor will stop and unblind the trial and perform the final analysis. Stopping rules for futility and efficacy and any additional details regarding the DMC can be found in the DMC Charter.

Each subject will have two stages of study participation: Treatment Period (Day 1 to Day 22) and Follow-up Period (Day 23 to Day 366).

The study procedures consist of four (4) clinic visits, and three (3) safety phone calls. After enrolment and vaccination on Day 1, all subjects will then return to the clinic for three (3) additional clinic visits, on Days 22, 181 and 366. During the study there will also be three (3) safety phone calls on Days 15, 91 and 271. Subjects participating in the solicited safety subset will receive an additional call on day 3 reminding them to complete their diary card.

Additionally, all subjects will receive weekly phone calls or messages to assess for primary protocol-defined ILI symptoms during the active ILI surveillance period, defined as from Day 1 through Day 181 or until the end of the influenza season, whichever is longer. The purpose of the ILI surveillance phone calls/message is to trigger a clinic or home visit to collect a nasopharyngeal swab. Subjects will also be asked for the duration of the trial (up to Day 366) to contact the site at the onset of ILI symptoms to schedule a clinic visit for NP swab collection.

After an initial screening, subjects will be vaccinated with a single dose of aQIV or non-influenza comparator on Day 1. Subjects will be observed for at least 30 minutes post-vaccination on Day 1 for any immediate reactions. A subset of randomly selected subjects from both treatment groups will be chosen to participate in a solicited safety subset. Subjects participating in the solicited safety subset will receive a Subject Diary along with instructions and training to ensure proper completion and assessment of reactogenicity. Each subject in the solicited safety subset will be instructed to document in their Subject Diary solicited local and systemic adverse events that may occur post-vaccination from Day 1 through Day 7. Subjects in the solicited safety subset will be asked to return their completed Subject Diary at their Day 22 clinic visit.

For all subjects, any unsolicited adverse event and concomitant mediation use, after vaccination from Day 1 to Day 22 will be collected at the Day 15 safety phone call and during the Day 22 clinic visit. Information collected at these visits will be documented in the subject's source records and captured in the Electronic Case Report Form (eCRF). All subjects will also receive an ILI booklet on Day 1, and will be instructed to measure their body temperature using the thermometer provided starting from onset day of primary protocol defined ILI to the day they come into the clinic for their NP swab collection. Subjects will be asked to return the ILI booklet at the time of their NP clinic visit.

During the remaining follow-up phase of the study, safety data including adverse events leading to withdrawal, AESI, NOCD and SAE and concomitant medication use related to these events will be captured via safety phone calls or clinic visits throughout the remainder of the trial (up to Day 366).

Subjects experiencing an ILI will have one (1) additional clinic visit and one (1) additional safety call: (1) a clinic or home visit to collect a nasopharyngeal swab as soon as possible within 3, but up to 6, days after the first day of onset of primary protocol-defined ILI symptoms, and (2) a safety follow-up call 30 days after ILI onset to determine if subsequent medically-attended adverse events occurred and if any concomitant medication associated with these adverse events were used. The use of anti-viral medications will be permitted after NP swab has been obtained and will be documented as concomitant medications. Nasopharyngeal swabs will be processed for viral culture

and RT-PCR confirmation. Culture positive samples will undergo antigenic characterization.

One season in which at least 2800 subjects are anticipated to be enrolled will be selected for the collection of immunogenicity samples. Samples from approximately 2800 subjects participating in the selected season will be collected at Day 1 (baseline) and Day 22 (visit 3). In order to maintain the study blind equal numbers of subjects from both treatment groups will be asked to provide blood specimens (see Section 3.5, Collection of Clinical Specimens). After all of the blood specimens have been obtained a subset of samples from those collected will be randomly selected on a 4:1 ratio (1,362 aQIV; 340 Boostrix) for the purpose of completing the analysis of the immunogenicity objectives. Serum samples from subjects with RT-PCR confirmed influenza, along with a subset of subjects who did not have RT-PCR confirmed influenza, may be tested to estimate the correlate of protection. The serologic component of the correlate of protection will be measured using either a validated haemagglutination inhibition (HI) and/or other immunological assays (such as microneutralization).

Study Case Definition of Influenza-Like-Illness

Two definitions of ILI will be used. Primary protocol-defined ILI will be used to trigger nasopharyngeal swab retrieval (Section 3.5, Collection of Clinical Specimens) and completion of the ILI booklet (Section 3.4.2, Tools Used for Data Collection). The respiratory symptoms in both definitions are considered a new onset or exacerbation of a pre-existing condition.

- *Primary protocol-defined ILI*: At least one of the following respiratory symptoms: sore throat, cough, sputum production, wheezing, or difficulty breathing; concurrently with at least one of the following systemic symptoms: temperature of > 37.2°C/ 99°F, chills, tiredness, headache, or myalgia.
- *Modified CDC ILI definition*: Fever (temperature of > 37.2° C/99°F) with cough or sore throat.

The ILI onset day is defined as the first day that the subject meets the primary protocol-defined ILI.

The ILI end date is defined as the date the last symptom resolves.

A new ILI episode will only be taken into account after resolution of the previous one, as judged by the investigator (suggested interval between two ILI episodes is 14 symptom-free days).

3.2 Study Period

Each subject should expect to participate in the study for approximately one year, from the time of enrolment through the last study visit.

3.3 Blinding Procedures

The trial is designed as an observer-blind study. Designated unblinded nurse(s) or physician(s) will be responsible for administrating the study vaccines to the subjects and will be instructed not to reveal the identity of the study vaccines either to the subject or the investigative site staff (i.e., investigator and study nurse) involved in the monitoring of conduct of the trial up until completion of the trial and final data review, except in a medical emergency. Vaccines will be selected and administered according to the Pack ID assigned to the subjects by IRT. Neither the subject nor any of the investigative staff who are involved in the treatments or clinical evaluation of the subject will be aware of the vaccine administered. Vaccine administration should be shielded from the subject and blinded study personnel. The unblinded personnel should not be involved in data collection such as safety assessments and/or physical assessment and should not access the blinded data entry fields. In case of an emergency, the Investigator can disclose the subject's assigned vaccine. The information can be retrieved from the IRT system either via web or phone (a 24/7 backup service).

Except in the case of medical necessity, a subject's treatment should not be unblinded without the approval of the Sponsor. In such instance of medical emergency, every effort should be made to contact the Sponsor prior to unblinding. If unblinding should occur (by either accidental unblinding or emergency unblinding for an SAE) prior to completion of the study, the investigator must promptly contact the Sponsor and document the circumstances on the appropriate forms. Instructions regarding emergency unblinding will be provided to the investigator.

All personnel involved in performing laboratory assays and others who are directly involved in the conduct of the trial or in the analysis of the final trial results will remain blinded to the treatment codes until at least the database has been locked for final analysis.

3.4 Data Collection

3.4.1 Data Collected from Subjects

The following data will be collected from each subject during their study participation:

- Medical History

- Vaccination History
- Demographic Information.
- Post-vaccination unsolicited AEs (from Day 1-22)
- Adverse Events
  - AEs leading to withdrawal
  - AESIs
  - NOCDs
  - SAEs
  - ILI
  - Medically-attended adverse events within 30 days after the ILI onset
- Concomitant Medications (as defined in Section 6.5)
- Reason for study termination
- Body temperature measurements from the onset of ILI until day of clinic visit for NP sample collection.

All data collected must only be identified using the Subject ID, as described in Section 5.1.4, Randomization.

The investigator will request a vaccination card or other documentation of previous vaccination history from the subject. If available, the card or other documentation will be copied and placed in the subject's file to serve as source documentation. If documentation of vaccination history is not available, the subject's verbal recall of prior vaccination of the subject will be recognized as sufficient medical history; this approach and the collected information must be captured in the source documentation.

3.4.2 Tools Used for Data Collection

ILI Booklet

Subject's experiencing an ILI will be asked to document their daily body temperature in an ILI booklet. An ILI booklet will be given to all subjects at their Day 1 visit. The booklet will be used to collect information on body temperature measurements which are to be completed daily (using the supplied thermometers) until the subject comes in for their NP sample collection. At the ILI clinic visit the subject will be asked to turn in their ILI booklet. A new booklet will be administered in case the subject experiences another ILI.

No corrections or additions to the information recorded by the subject or legal guardian within the ILI booklet will be allowed after it is delivered to the site. Any blank or illegible fields on the ILI booklet must be described as missing in the eCRF.

Subject Diary

Subjects participating in the solicited safety subset will be given a paper diary at their Day 1 clinic visit to complete. The paper diaries (pDiaries) to be completed by subjects participating in the solicited safety subset, hereafter referred to as Subject Diaries, will be the only source document allowed for solicited local and systemic adverse events (including body temperature measurements), starting after the initial 30 minute post-vaccination period at the clinic through Day 7.

At the Day 22 clinic visit subjects participating in the solicited safety subset are to return their completed diary and the site staff should review the completed diary with them. The following additional rules apply to documentation of safety information collected in the Subject Diary.

1. No corrections or additions to the information recorded by the subject or legal guardian within the Subject Diary will be allowed after it is delivered to the site.

2. Any blank or illegible fields on the Subject Diary must be described as missing in the CRF.

Case Report Forms

This study utilizes Electronic Case Report Forms (eCRFs) to collect study-related data from each subject. A qualified site staff member(s) is required to enter subject data in the eCRFs in English based on the medical information available in each subject's source record.

Data should be entered into the eCRF in a timely fashion following each subject's clinic visit, study procedure, or phone call. Each subject's eCRF casebook will be compared with the subject's source records by a Seqirus-approved study monitor (or designee) over the duration of the study in order to ensure data collection accuracy.

The following additional rules apply to documentation of Subject Diary information collected in the CRFs:

1. The site must enter all readable entries in the Subject Diary into the CRF, including those values that may be biologically implausible (e.g. body temperature: 400°C).
2. Any illegible or implausible data should be reviewed with the subject or legal guardian. If an underlying solicited or unsolicited adverse event is described on

review with the subject, this should be described in the source document and reported as an unsolicited adverse event in the Adverse Event CRF (e.g., if the subject above confirms body temperature of 40°C on the day in which body temperature: 400°C was written into his/her Subject Diary, this fever of 40°C should be recorded in the Adverse Event CRF).

3. Any newly described safety information (including a solicited adverse event) must not be written into the Subject Diary and must be described in the study file as a verbally reported adverse event. Any adverse event reported in this fashion must be described as an unsolicited adverse event and therefore entered on the Adverse Event CRF.

3.5 Collection of Clinical Specimens

The following clinical specimens are required to be collected from each subject in this study:

- Nasopharyngeal swabs (as needed from subjects experiencing symptoms that meet primary protocol-defined ILI criteria).

The following clinical specimens are required to be collected from subjects participating in the immunogenicity subset:

- Blood at the Day 1 and 22 clinic visit

Collection and processing of each specimen should be completed by a qualified site member and in accordance with the study-specific Laboratory Manual. Testing of clinical specimens will be performed by a Seqirus or designated laboratory. Refer to the study-specific Laboratory Manual for additional details.

Blood Specimens

Approximately 10 mL sample of blood will be drawn from approximately 2800 subjects participating in the immunogenicity season at Days 1 and 22. The blood volume will not exceed 10 mL at each time point in order to provide the necessary serum volume (approximately half of the blood draw volume) for the serology assays (see Section 7, Assessments for additional details).

The total amount of blood collected over the study period per subject will be approximately 20 mL.

Nasopharyngeal Swabs

Subjects, who from Visit 1 (Day 1) onwards, experience symptoms meeting the primary protocol-defined ILI criteria (i.e. at least one of the following respiratory symptoms (new onset or exacerbation of pre-existing condition): sore throat, cough, sputum production,

wheezing, or difficulty breathing concurrently with at least one of the following systemic symptoms: temperature of > 37.2°C/ 99°F, chills, tiredness, headache, or myalgia), will have one NP swab collected for evaluation of the presence of influenza virus by RT-PCR. The NP swab will be collected as soon as possible within 3 days of ILI onset, but collection up to 6 days will be permitted.

All samples will also be cultured for the growth of the strain of influenza obtained from the subjects in order to conduct antigenic characterization (to determine whether the clinical isolate is antigenically matched or antigenically unmatched to the vaccine strain).

3.6 Stopping/Pausing Guidelines

NP swabs will be analyzed in batches on a rolling basis throughout the study. When the number of RT-PCR confirmed influenza cases is between 119 and 238 interim analyses for efficacy and futility will be performed by an independent DMC. At least one interim analysis will be performed based on the number of RT-PCR confirmed influenza cases accrued at the time of the first interim analysis. After periodic review of safety and efficacy data, the DMC will make a recommendation as to whether enrolment in the study should continue, be stopped or paused (see Section 8.6 Interim Analysis).

Independent of the DMC, the Sponsor can halt the study at any time. If the study is halted, the Sponsor will promptly notify the health authorities and investigators, who will promptly inform the study subjects and local Ethics Committee/ Institutional Review Board (EC/IRB) as per local regulations. Study vaccinations and further enrolment will only occur after written authorization is provided by the Sponsor in conjunction with a recommendation to proceed by the DMC and in consultation with the health authorities and EC/IRB, as appropriate.

3.7 Data Monitoring Committee

An independent DMC will be constituted for this trial. The members of the DMC shall have no involvement in the design or conduct of the trial and no financial interest in the outcome of the trial. The DMC will comprise solely of non-Seqirus employees, and include medical experts and a biostatistician. The main purpose of the DMC will be to monitor study progress and ensure the safety of subjects on an ongoing basis during the trial. In addition, DMC will provide recommendation on stopping the study for either efficacy or futility after unblinded review of efficacy data in a pre-planned interim analysis.

Unblinded interim analyses for efficacy and futility will be executed by the DMC, if the number of RT-PCR confirmed influenza cases is between 119 and 238. In addition, the DMC will also review blinded, and if requested, semi-or fully-unblinded safety data at

pre-specified intervals during the study. Another interim analysis might be recommended before target 238 cases are observed. Any unblinded data will be reviewed in closed sessions of the DMC, without participation of the Sponsor. All descriptions of these closed sessions will be unavailable to the Sponsor until study unblinding has occurred. All reports, following open sessions of blinded data review will be available to the Sponsor as appropriate. DMC recommendations will be expressed clearly to the Sponsor, at minimum in written communication.

After reviewing safety and efficacy data, the DMC will recommend that enrolment be continued, halted temporarily (pending additional information from the Sponsor or modification to the study design) or halted permanently as specified in the DMC charter.

The DMC charter will be written to clearly describe the operational processes and the roles and responsibilities, including the timing of meetings, methods of providing information to and from the DMC, format and content of data to be reviewed, frequency and format of meetings, and membership requirements.

3.8 Premature Withdrawal from Study

Subjects may withdraw at any time, or be dropped from the study at the discretion of the investigator should any untoward effects occur and/or for safety reasons. In addition, a subject may be withdrawn by the investigator or the Sponsor if he/she violates the study plan or for administrative reasons. The investigator or study coordinator must notify the Sponsor immediately when a subject has been withdrawn due to an adverse event.

The circumstances above are referred to as premature withdrawal from the study, and the reason for premature withdrawal should be clearly documented and detailed in the source documentation. The investigator should make every attempt to evaluate the subject's safety, including resolution of ongoing AEs, at the time of premature withdrawal. If a subject wants to withdraw from the study prior to the last planned study visit, the subject will be asked to be followed for safety for the duration of the study. If an enrolled subject withdraws from the study before receiving vaccine they will be considered an early withdrawal but no further study procedures will be performed. When a subject withdraws, or is withdrawn, from the study, the procedures described in Section 5.5.1, Early Termination Visit should be completed if possible. Withdrawn subjects will not be replaced.

The reasons for premature withdrawal from the study include: Adverse event, death, withdrawal of consent, lost to follow-up, administrative reason, and protocol deviation. These reasons are described in greater detail below.

Adverse Event

For any subject withdrawn from study participation prior to the planned Study Termination Visit, it is important to determine if an AE was associated with the reason for discontinuing the study. This AE must be identified on the AE CRF page by indicating "Withdrawn from study due to AE". Any ongoing AEs at the time of study withdrawal must be followed until resolution or stabilization.

If a medically attended adverse event occurred within 30 days following a primary protocol definition of ILI, the event should also be reported on the AE eCRF page (see Section 7.2, Efficacy Assessment).

Death

For any subject withdrawn from study participation due to death, this should be noted on the Study Termination eCRF page and the associated SAE that led to the death must be reported (see Section 7.2, Efficacy Assessment).

Withdrawal of consent

A subject or legal guardian can withdraw consent for participation in the study at any time without penalty or loss of benefit to which the subject is otherwise entitled. Reason for early termination should be deemed as "withdrawal of consent" if the subject withdraws from participation due to a non-medical reason (i.e., reason other than AE). If the subject or legal guardian intends to withdraw consent from the study, the investigator should clarify if the subject will withdraw completely from the study or if the subject will continue study participation for safety, or a subset of other study procedures. If the subject requests complete withdrawal from the study, no further study interventions will be performed with the subject.

In countries where the Health Insurance Portability and Accountability Act (HIPAA) is applicable, if a subject or legal guardian withdraws consent but does not revoke the HIPAA authorization, the Sponsor will have full access to the subject's medical records, including termination visit information. If a subject or legal guardian revokes only the HIPAA authorization, the Sponsor will have full access to all of the subject's medical records prior to the date and time of written revocation.

Lost to Follow-Up

For subjects who fail to show up for final visits (clinic or telephone contacts), or for three consecutive visits, study staff are encouraged to make at least three documented attempts to contact the subject by telephone and at least one documented written attempt to contact

the subject or legal guardian to encourage the completion of study termination procedures. These efforts to contact the subject should be recorded in the source document. The termination date for the subject to be captured on the Study Termination eCRF page is the date of the last successful contact (clinic visit or telephone) with the subject.

Administrative Reason

Examples for subjects withdrawn from the study due to administrative reason can include: Sponsor decision to terminate the study, subject meeting a pre-specified withdrawal criterion, subject discontinuation for insurance issues, moving, no time, etc. This reason should be noted in the Study Termination eCRF page and any ongoing AEs at the time of study withdrawal must be followed until resolution/stabilization.

If the clinical study is prematurely terminated by the Sponsor, the investigator is to promptly inform the study subjects and local EC/IRB and should assure appropriate therapy and follow up for the subjects. All procedures and requirements pertaining to the archiving of study documents should be followed. All other study materials (study medication/vaccines, etc.) must be returned to the Sponsor.

For subjects who are withdrawn from the study due to receipt of an excluded medication/vaccination or due to significant protocol non-compliance, this reason should be noted in the Study Termination CRF page.

Protocol Deviation

A protocol deviation is any change, divergence, or departure from the study design or procedures of a study protocol. In general, subjects associated with protocol deviations may remain in the study unless continuation in the study jeopardizes the subject's health, safety, or rights.

Investigators will apply due diligence to avoid protocol deviations. Under no circumstances should the investigator contact Seqirus or its agents, if any, monitoring the study to request approval of a protocol deviation, as no authorized deviations are permitted. If the investigator feels a change to the protocol would improve the conduct of the study this must be considered a protocol amendment, and unless such an amendment is agreed upon by Seqirus and approved by the IRB/EC and health authorities it cannot be implemented.

3.9 End of Study

Evaluation of the primary efficacy objective requires the testing of biological samples from the study subjects, which can only be completed after all samples are collected. Nasopharyngeal swabs may be collected up to Day 366. For the purpose of this protocol, end of study is defined as the completion of the testing of such biological samples, to be achieved no later than 8 months after collection of the last biological sample visit 7 (Day 366).

4. SELECTION OF STUDY POPULATION

4.1 Inclusion Criteria

In order to participate in this study, all subjects must meet ALL of the inclusion criteria described.

1. Males and females ≥ 65 years old who are healthy or have co-morbidities (see Table 5.1.2-1).
2. Individuals who or whose legal guardian have voluntarily given written consent after the nature of the study has been explained according to local regulatory requirements, prior to study entry.
3. Ability to attend all scheduled visits and to comply with study procedures including follow-up[5] (and responding to messages and telephone contact).

4.2 Exclusion Criteria

Each subject must not have:

1. Receipt of diphtheria or tetanus toxoid or pertussis (acellular or whole cell) vaccines within the previous 5 years.
2. History of behavioral or cognitive impairment or psychiatric condition that, in the opinion of the investigator, may interfere with the subject's ability to participate in the study.
3. History of any medical condition considered an adverse event of special interest, see Section 7.1.4.1, Adverse Events of Special Interest.
4. Progressive or severe neurological disorder, seizure disorder, or history of Guillain-Barré syndrome.
5. Hypersensitivity, including allergy, to any component of vaccines see Table 6.1-1 and Table 6.1-2, medicinal products or medical equipment whose use is foreseen in this study.
6. Encephalopathy (e.g. coma, decreased level of consciousness, prolonged seizures) within 7 days of administration of a previous pertussis antigen-containing vaccine.

[5] A subject or legal guardian is considered to be compliant if the Investigator judges that the subject will complete the Subject Diary when applicable, return for all the follow-up visits, and be available for telephone calls as scheduled in the study.

7. Clinical conditions representing a contraindication to intramuscular vaccination and blood draws, including bleeding diathesis, or any other condition that may be associated with prolonged bleeding.
8. Abnormal function of the immune system resulting from:
   a. Clinical conditions.
   b. Systemic administration of corticosteroids (PO/IV/IM) at a dose equivalent to 20 mg of prednisone for more than 14 consecutive days within 90 days prior to informed consent.
   c. Administration of antineoplastic and immunomodulating agents (e.g. TNF α antagonists or anti-B cell antibodies) or radiotherapy within 1 year prior to informed consent.
9. Receipt of immunoglobulins or any blood products within 180 days prior to informed consent.
10. Receipt of an investigational or non-registered medicinal product within 30 days prior to informed consent or before completion of the safety follow-up period in another study and who are unwilling to refuse participation in another clinical study at any time during the conduct of this study (note: concomitant participation in an observational study not involving drugs, vaccines, or medical devices, is acceptable).
11. Study personnel or immediate family members (brother, sister, child, parent), the spouse of study personnel or individuals who are financially or emotionally dependent on study staff
12. Receipt of any influenza vaccine within 6 months prior to enrolment in this study or who plan to receive influenza vaccine while participating in the study.
13. Receipt of any inactivated vaccine 14 days or live-attenuated vaccine 28 days prior to enrolment in this study or who are planning to receive any vaccine within 28 days from study vaccination.
14. Fever at the time of screening, defined as oral temperature ≥38.0 degrees Celsius (≥ 100.4° F). Enrolment could be considered if fever is absent for 72 hours.
15. Signs or symptoms of acute respiratory tract infection at the time of screening. Enrolment could be deferred if signs and symptoms are absent for 72 hours.
16. Residence in a chronic care facility (e.g. nursing home).
17. Participation in this trial in a prior season, if applicable.
18. Fatal prognosis of an underlying medical condition (<12 months life expectancy).

19. Any other clinical condition that, in the opinion of the investigator, might interfere with the results of the study or pose additional risk to the subject due to participation in the study.

4.3 Criteria for Delay of Vaccination

There may be instances when individuals meet all eligibility criteria for vaccination yet have a transient clinical circumstance which may warrant delay of vaccination: fever [≥38.0° C (≥ 100.4° F), signs or symptoms of acute respiratory tract infection or use of antipyretics and/or analgesic medications within 24 hours prior to vaccination. Under such circumstances, a subject may be considered eligible for study enrolment after the 72 hours have passed and inclusion/exclusion criteria have been rechecked, and if the subject is confirmed to be eligible.

5. STUDY PROCEDURES

The sections that follow provide an overview of the procedures that are to be followed in enrolling, evaluating, and following subjects who participate in this clinical study. Visits can be either clinic visits or safety follow-up telephone calls, as specified in the Table below and in the Time and Events Table 2, 3 and 4.

Table 5-1: Study Procedures

Visit Category	Procedures
Vaccination Clinic Visit – Pre-vaccination Procedures	Section 5.1. describes procedures to be followed prior to study vaccination: informed consent, screening, enrolment, and randomization
Vaccination Clinic Visit(s) – Vaccination and Post-vaccination Procedures	Section 5.2 describes procedures to be followed during each clinic visit involving vaccination: vaccination, post-vaccination procedures, and post-vaccination reminder calls
Post-vaccination Visit(s)	Section 5.3 describes follow-up clinic visits, safety follow-up calls, and active ILI surveillance calls
Unscheduled Visit(s)	Section 5.4 describes possible procedures to be followed at unscheduled clinic visits
Study Termination Visit	Section 5.5 describes procedures to be followed at the last study visit for a subject (may include early termination visit)

5.1 Vaccination Clinic Visit - Pre-vaccination Procedures

This section describes the procedures that must be performed for each potential subject prior to vaccination, including obtaining informed consent, screening, enrolment and randomization. Please refer to Time and Events Table 2.

5.1.1 Informed Consent

"Informed consent" is the voluntary agreement of an individual or his/her legal guardian(s) to participate in research. Consent must be given with free will of choice, and without undue inducement. The individual must have sufficient knowledge and understanding of the nature of the proposed research, the anticipated risks and potential benefits, and the requirements of the research to be able to make an informed decision.

Informed consent following local IRB/EC guidance **must** be obtained before conducting any study-specific procedure (i.e., all of the procedures described in the protocol). The process of obtaining informed consent should be documented in the subject source document in addition to maintaining a copy of the signed and dated informed consent.

If a subject or legal guardian is unable to read, an impartial witness should be present during the entire informed consent discussion. An impartial witness is defined as a person who is independent from study conduct, who cannot be unfairly influenced by those involved with the study, who attends the informed consent process if the subject or, if applicable, the subject's legally acceptable representative cannot read, and who reads the informed consent form (ICF) and any other written information supplied to the subject. After the written ICF and any other written information to be provided to subjects, is read and explained to the subject or legal guardian and after the subject or legal guardian has verbally consented to the subject's participation in the study and, if capable of doing so, has signed and personally dated the ICF, the witness should sign and personally date the consent form. By signing the consent form, the witness attests that the information in the consent form and any other written information was accurately explained to, and apparently understood by, the subject or legal guardian and that informed consent was freely given by the subject or legal guardian.

The informed consent process may be conducted within 10 days prior to Day 1.

5.1.2 Screening

After an individual has consented to participate in the study and informed consent is signed, that individual will be given a unique Screening Number. The subject's unique Screening Number will be documented in the Screening and Enrolment log. The eligibility of the subject will be determined based on the inclusion and exclusion criteria listed in Section 4, Selection of Study Population and evaluated during this screening procedure.

Prior to study enrolment, demographic data will be collected from the subject, including: age, sex, race, ethnicity, height and weight, prior influenza vaccination, smoking status and, comorbidity and risk of complications from influenza indicated by a calculated score. The risk assessment which incorporates medical comorbidity among other baseline characteristics is a validated predictor of risk of complications from influenza in subjects ≥65 years of age (Hak, 2004) (see Table 5.1.2-1, Prediction Rule for Estimating the Probability of Hospitalization Due to Pneumonia or Influenza and Death Due to Any Cause). Using this model, a score of <50 is considered low risk and a score of ≥ 50 is considered high risk.

It is important to note that the determination of pre-existing medical conditions, for the purpose of calculating the risk score, should be made by the investigator based on his or her clinical judgment. A list of conditions which are associated with increased risk of complications from influenza are presented in Appendix 1 as a reference for the Investigator (Website CDC and Mullooly et al., 2007).

Table 5.1.2-1: Prediction Rule for Estimating the Probability of Hospitalization Due to Pneumonia or Influenza and Death Due to Any Cause (Hak, 2004)

Characteristic	Score[a]
Age, years	
<70	0
70-74	14
75-79	28
80-89	42
≥90	56
Sex	
Female	0
Male	9
Outpatient visits during the previous year	
0	0
1-6	11
7-12	22
>13	33
Previous hospitalization due to pneumonia or influenza	
No	0
Yes	63
Comorbidity[b]	
Pulmonary disease	18
Heart disease	6
Renal disease or renal transplant	12
Dementia or stroke	22
Non-hematological and hematological cancer	48

Notes:
[a] The prognostic score for a given subject can be obtained by adding the scores for each applicable characteristic.
[b] Pre-existing medical conditions of eligible subjects will be scored following judgment by the investigator. Appendix 1 provides a list of conditions with examples to provide guidance to the investigator.

Medical history will also be collected, including but not limited to any medical history that may be relevant to subject eligibility for study participation such as prior vaccinations, concomitant medications, and previous and ongoing illnesses or injuries. Relevant medical history should also include any medical history that contributes to the

understanding of the risk score and of an adverse event that occurs during study participation, if it represents an exacerbation of an underlying disease/pre-existing problem.

Review of systems is a structured interview that queries the subject or legal guardian as to any complaints the subject has experienced across each organ system. This will be performed before enrolment and used to guide physical examination.

If applicable, prior and concomitant medications or vaccinations taken prior to start of study should be collected (refer to Section 6.5, Prior and Concomitant Medications and Vaccines for further details).

Collection of vital signs is to be performed: heart rate, blood pressure, respiratory rate and pre-vaccination body temperature (preferably oral). If body temperature is ≥38.0°C (or ≥100.4°F) at the time of screening, vaccination must be postponed until 3 days after the fever has resolved (see Section 4.3, Criteria for Delay of Vaccination).

Measure height and weight. Measurement and recording of vital signs, height, weight and body temperature, may be conducted by a trained health care professional.

A general physical examination is to be performed by a qualified health care practitioner. "Qualified health care practitioner" refers to any licensed health care professional who is permitted by institutional policy to perform physical examinations and who is identified within the Study Staff Signature Log.

The data described above will be written in the source document (see Section 9.1, Source Documentation). Should the physical assessment reveal any abnormal values or events, these must be documented as part of medical history.

Prior to vaccination, approximately10 mL of blood will be drawn from approximately 2800 subjects participating in the immunogenicity season (see Section 3.5, Collection of Clinical Specimens).

In the event that the individual is determined ineligible for study participation, he/she is considered a screen failure. The reason for screen failure must be documented in the Screening and Enrolment log. If the individual is determined to be eligible for the study, he/she will be enroled into the study.

5.1.3 Enrollment

After signing the ICF, if an individual is determined to be eligible for study participation, the investigator or delegate will enroll the subject and enter subject information and stratification information into the Interactive Response Technology (IRT) system.

5.1.4 Randomization

Enroled subjects will be randomized in the IRT system by a 1:1 ratio to receive either aQIV or the non-influenza comparator vaccine Boostrix® and will be automatically assigned a unique Subject ID and Pack ID indicating the assigned treatment. The Subject ID will be the subject's unique identification number for all CRFs and associated study documentation that will be used for duration of the study. The Subject ID consists of a 7-digit number resulting from the combination of the site number, and the subject's order of randomization at the site. After randomization, the Screening Number ceases to be used and remains in the Screening and Enrolment Log only. The list of randomization assignments is produced by the IRT service provider and approved by Seqirus or delegate.

Randomization will be stratified by age (cohorts 65 to 74 years and 75 years and above), study site and also based on risk for complications from influenza (assessment score < 50 or ≥50).

If for any reason, after signing the ICF, the subject who is eligible and enroled fails to be randomized, this is called a randomization failure. Further guidance is provided in the CRF Instructions. The reason for all randomization failures should be recorded in the Screening and Enrolment Log and in the source document as specified in the Source Data Agreement (SDA). The information on subjects who are randomization failures should be kept distinct from subjects who are screen failures, as described in Section 5.1.2, Screening.

If for any reason, after randomization the subject fails to undergo treatment, this is an Early Termination and the reason should be recorded in source document as specified in the SDA. The information on these Early Termination subjects should be kept distinct in the source documentation from randomization failures.

Subjects from a single season will have blood samples collected for inclusion in an immunogenicity subset. Samples from approximately 2800 subjects participating in the selected season will be collected at Day 1 (baseline) and Day 22 (visit 3). In order to maintain the study blind equal numbers of subjects from both treatment groups will be asked to provide blood specimens (see Section 3.5, Collection of Clinical Specimens). The IRT-system will be used to identify subjects from which blood specimens are to be collected. After all of the blood specimens have been collected a randomly selected subset of these samples will be analyzed. Detailed information regarding the randomization procedures associated with the selection of the samples to be analyzed can be found in the Statistical Analysis Plan (SAP).

A subset of approximately 2,100 subjects from multiple seasons and countries participating in the trial will be randomly selected for participation in the solicited safety subset. Equal numbers of subjects from both treatment arms will be selected for participation in this subset. Detailed information regarding the randomization procedures associated with the selection of the subjects participating in this subset can be found in the Statistical Analysis Plan (SAP).

5.2 Vaccination Clinic Visit – Vaccination and Post-vaccination procedures

Please refer to Time and Events Table 2. Vaccination will be performed on Day 1 using the vaccine identified by the assigned Pack ID.

The Day 1 serology sample collected from selected subjects participating in the immunogenicity season must be taken **prior** to vaccination.

After completing the pre-vaccination procedures as described in Section 5.1, Vaccination Clinic Visit - Pre-vaccination Procedures, the vaccine will be administered to the subject according to the procedures described in Section 6.3, Vaccine Preparation and Administration, observing the blinding procedures described in Section 3.3, Blinding Procedures.

Prior to administration of the study vaccination, it needs to be confirmed that the subject is eligible for vaccination and does not meet any criteria for exclusion or delaying study vaccination as described in Section 4, Selection of Study Population.

5.2.1 Post-vaccination Procedures

The following post-vaccination procedures will be performed on Day 1.

Observation Period

After vaccination, the subject will be observed for at least 30 minutes for unsolicited adverse events, solicited adverse events, and a body temperature measurement (preferably oral) will be taken. During this observation period, the subject should be trained on how to use the thermometer and for subjects participating in the solicited safety subset, the ruler provided and how to measure local solicited adverse events (see Section 7.1.1, Solicited Adverse Events). All safety data collected during this time should be recorded in the subject's source document.

Subject Diary Training

A Subject Diary will be dispensed to subjects participating in the solicited safety subset to document solicited adverse events from Day 1 to Day 7. The Subject Diary is the only

source for collection of these data; therefore, it is critical that the subject completes the Subject Diary correctly. The subject should be trained on how and when to complete each field of the Subject Diary. The Subject Diary should be completed on a daily basis and the entries should be written clearly in pen. See additional rules in Section 3.4.2, Tools Used for Data Collection.

The subject or legal guardian should be trained on how to self-measure local solicited adverse events and body temperature (preferably oral). The measurement of solicited local adverse events is to be performed using the ruler provided by the site.

The subject or legal guardian should be instructed how to perform body temperature measurement using the thermometer provided by the site. If the subject feels unusually hot or cold during the day, the subject or legal guardian should check body temperature. If the subject has fever, the highest body temperature observed that day should be recorded in the Subject Diary.

Subject Diary completion starts on the day of vaccination. The subject will be instructed to check for solicited adverse events approximately 6 hours after the vaccination or prior to going to bed. Entries on subsequent days should be performed around the same time, preferably in the evening.

Subject Diary training should be directed at the individual(s) who will perform the measurements of adverse events and who will enter the information into the Subject Diary. In some situations, the Subject Diary may be completed by somebody other than the subject or legal guardian (except study site personnel). If a person other than the subject or legal guardian enters information into the Subject Diary, the reason that the subject cannot complete their own Subject Diary and the person's identity and relationship to the subject must be documented in the Subject Diary. Any individual that makes entries into the Subject Diary must receive training on completion of the Subject Diary at the time of the visit. This training must be documented in the subject's source record.

The same individual should complete the Subject Diary throughout the course of the study.

Plan Next Study Activities

The site should schedule the next study activity with the subject or legal guardian. It is recommended for the site to already schedule in advance the remaining upcoming study activities.

Discharge

The subject or legal guardian should be reminded to contact the site if there are any questions, and to contact the site immediately (or as soon as the subject is medically stable) if the subject has a medical condition that leads to a hospitalization or an emergency room visit or to a visit to/by a doctor or is otherwise of concern.

An ILI instruction sheet will be provided with instructions for reporting possible ILIs. The subject or legal guardian will be reminded to contact the site immediately if the subject experiences symptoms meeting primary protocol-defined ILI criteria in order to have a NP swab collected for evaluation of the presence of influenza virus. If anti-viral medications (e.g. neuraminidase inhibitors) are prescribed it is recommended that an NP swab be obtained prior to the first dose.

An ILI booklet will be dispensed to document, in case of a protocol-defined ILI, the subject's daily body temperature. The subject or legal guardian will be instructed to start recording the subject's daily body temperature (preferably oral) daily from protocol-defined ILI onset day until the day the subject comes in to the clinic for their NP sample collection. Subjects will be asked to return the ILI booklet at the time of their ILI clinic visit. At the ILI visit the subject's will be given a new ILI booklet in case they experience another ILI.

Completion instructions should be directed at the individual(s) who will enter the information into the ILI booklet. In some situations, the ILI booklet may be completed by somebody other than the subject or legal guardian, except study site personnel. If a person other than the subject or legal guardian enters information into the ILI booklet, the reason that the subject cannot complete the ILI booklet and the person's identity and relationship to the subject must be documented in the ILI booklet. Any individual that makes entries into the ILI booklet must receive completion instructions at the time of the clinic visit. In some countries based on local requirements and practices subjects may also be given a subject identification card which will contain emergency contact information.

5.2.2 Post-vaccination Reminder Calls

Subject Diary Reminder Calls

Subjects participating in the solicited safety subset will receive a diary reminder call on Day 3. The purpose of this call is to remind the subject or legal guardian about completion of the Subject Diary. The call follows the Subject Diary Reminder Phone Call Script provided to the site. The subject or legal guardian should be reminded to contact the site via the telephone number provided in the informed consent to discuss medical questions.

The reminder call is not intended to be an interview for collection of safety data. If the subject or legal guardian wishes to describe safety-relevant information, the call should be continued by a healthcare professional from the study site, and the safety data should be recorded in the subject's medical chart.

5.3 Post-vaccination Visit(s)

Please refer to Time and Events Table 2 and 3. Post-vaccination visits will be performed on Days 15, 22, 91, 181, 271 and 366. In the event that a scheduled or unscheduled visit or call/message coincides, procedures may be combined.

5.3.1 Follow-up Clinic Visit(s)

Safety follow-up clinic visits will be performed on Days 22 and 181.

During the follow-up clinic visit on Day 22, for subjects participating in the solicited safety subset, the Subject Diary will be reviewed and collected. No changes to the information recorded within the Subject Diary are permissible. For details on the Subject Diary see Sections 3.4.2, Tools Used for Data Collection and 5.2.1, Post-vaccination Procedures. The subject or legal guardian will be interviewed to determine if any unsolicited adverse events (including SAEs, ILIs, NOCDs, AEs leading to withdrawal and AESIs) occurred and if any concomitant medications or vaccines were taken/ received during the time since the last clinic visit. This interview will follow a script which will facilitate the collection of relevant safety information. The healthcare professional reviewing these data will discuss the symptoms (if any) reported by the subject and will determine if any additional diagnoses and/or adverse events are present. All adverse events reported by the subject or legal guardian at this follow-up clinic visit must be recorded in the subject's source document and on an Adverse Events CRF, as specified in Section 7.1, Safety Assessment, and not written on the script used for the interview.

During the follow-up clinic visit on Day 181, the subject will be interviewed to obtain information relating to a subset of unsolicited AEs (all SAEs, ILIs, NOCDs, AEs leading to withdrawal and AESIs) and use of medication to treat these.

During both follow-up clinic visits, the subject will be asked as to whether he or she was hospitalized or was evaluated at an emergency room or a physician's office for any illness since the site's last contact with the subject. If an SAE has been identified by the site staff during the interview which has not previously been reported by the subject, this SAE will be reported by the site within 24 hours to Seqirus or delegate. Any additional relevant medical history will be recorded as needed.

During both follow-up clinic visits, an ILI assessment will be performed to determine if symptoms of ILI are present. Potential ILI symptoms will be documented in the subject's source records. If the onset of the ILI is 6 days or less before the visit, a NP swab should be collected from the subject for influenza testing and study staff will document the ILI on an Adverse Event and ILI CRF (see procedures described in Section 5.4, Unscheduled Visits).

During both follow-up clinic visits, a brief symptom-directed physical examination will be performed by a qualified health care practitioner according to symptoms the subject has reported. This physical examination will include an examination of organ systems that are considered relevant by the investigator based on review of the subject's reported adverse events, and concomitant medication use. This assessment may include measurement of vital signs (respiratory rate, blood pressure and heart rate), body temperature (preferably oral) and a check of general appearance. The physical assessment must be performed by the investigator or designee of the investigator, who is qualified to perform a physical assessment in accordance with their institutional policy. Measurement and recording of vital signs and body temperature may be conducted by a trained health care professional. Corresponding information is documented in the subject's source document and eCRF(s).

During the Day 22 follow-up clinic visit, approximately 10 ml of blood will be drawn from selected subjects participating in the immunogenicity season (see Section 3.5, Collection of Clinical Specimens).

The site should also schedule the next study activity, the safety call, with the subject or legal guardian. It is recommended for the site to also schedule in the remaining upcoming study activities whenever possible.

The subject or legal guardian will receive a written reminder of the next planned study activity. The subject or legal guardian will be reminded to contact the site immediately (or as soon as the subject is medically stable) if the subject has a medical condition that leads to a hospitalization, an emergency room visit, or a visit to/by a doctor, or is otherwise of concern.

The subject or legal guardian will be reminded to contact the site immediately if the subject experiences symptoms meeting primary protocol-defined ILI criteria in order to have a NP swab collected for evaluation of the presence of influenza virus. If anti-viral medications (e.g. neuraminidase inhibitors) are prescribed it is recommended that an NP swab be obtained prior to the first dose.

5.3.2 Safety Follow-up Calls

Safety follow-up calls will be performed on Days 15, 91 and 271.

Safety follow-up calls are calls made to the subject by a healthcare professional designated on the site log. These calls will follow a script which will facilitate the collection of relevant safety information. The subject or legal guardian will be interviewed according to the script. On Day 15, information will be collected regarding all unsolicited adverse events and concomitant medications or vaccinations associated with those events. Safety follow-up calls performed on Days 91 and 271 will collect information relating to a subset of unsolicited adverse events including SAEs, adverse events of special interest (AESIs), AEs leading to withdrawal, new onset of chronic disease (NOCD), ILI and concomitant medications or vaccinations associated with those events. All safety information described by the subject must be written down in a designated location within the source document and not written on the script used for the telephone call.

The subject will be asked as to whether he or she was hospitalized or was evaluated at an emergency room for any illness since the site's last contact with the subject. If an SAE has been identified by the site staff during the interview which has not previously been reported by the subject, this SAE will be reported by the site within 24 hours to Seqirus or delegate. Any additional relevant medical history will be reported to Seqirus or delegate and recorded as needed.

ILI assessments will be performed to determine if symptoms of ILI are present. If the subject reports during phone contact that a medical event has occurred with symptoms consistent with an ILI, the subject will be asked to visit the site for further evaluation and potential NP swab taking. An NP swab should be collected, for evaluation of the presence of influenza virus, preferably within 3, but up to 6, days after the first day of onset of ILI symptoms. See procedures described in Section 5.4, Unscheduled Visits.

The subject or legal guardian will receive a reminder of the next planned study activity. The subject or legal guardian will be reminded to contact the site immediately (or as soon as the subject is medically stable) if the subject has a medical condition that leads to a hospitalization or an emergency room visit or to a visit to/by a doctor or is otherwise of concern.

The subject or legal guardian will be reminded to contact the site immediately if the subject experiences symptoms meeting primary protocol-defined ILI criteria to have a NP swab collected for evaluation of the presence of influenza virus. If anti-viral medications (e.g. neuraminidase inhibitors) are prescribed it is recommended that an NP swab be obtained prior to the first dose.

5.3.3 Active Influenza Surveillance Phone Calls/Messages

Active surveillance for ILI for each subject will be conducted weekly either via telephone contacts or message from Day 1 to Day 181, or until the end of the influenza season, whichever is longer. The subject will be asked via phone/message a scripted set of questions to determine if symptoms of ILI are present. The purpose of the phone call/message is to trigger a clinic (or home) visit and a NP swab sample collection if ILI symptoms are present. Should ILI symptoms be present, the subject will also be reminded to complete the ILI booklet. Neither phone calls nor message are intended to collect any clinical data. Site personnel's follow up on all cases meeting primary protocol-defined ILI criteria is to be documented in the subject's source records and monitored in order to ensure that all subjects with ILI symptoms are scheduled for the NP swab sample collection visit as soon as possible within 3, but up to 6, days after the first day of onset of ILI symptoms. Data collected will be monitored by the study monitors in order to ensure adherence to the study protocol.

The subject will also be reminded to contact the site immediately if he or she experiences symptoms meeting primary protocol-defined ILI criteria to have a NP swab collected for evaluation of the presence of influenza virus. If anti-viral medications (e.g. neuraminidase inhibitors) are prescribed it is recommended that an NP swab be obtained prior to the first dose.

5.4 Unscheduled Visits

Please refer to Time and Events Table 4. An unscheduled visit describes a non-routine study visit triggered by a specific event. These could include anticipated or unanticipated adverse events or interventions.

5.4.1 Subjects Meeting the Influenza-Like-Illness Criteria

Clinic Visit or Home Visit – Obtaining NP Swab

Subjects will be asked to come to the site for an unscheduled clinic visit when experiencing symptoms meeting the primary protocol-defined ILI criteria. In the exceptional case that a clinic visit is not feasible, a home visit may be considered. The visit should occur as soon as possible within 3, but up to 6, days after the first day of onset of ILI symptoms. During the visit the following procedures should be carried out:

- Assess ILI symptoms and assess associated medication. Document any anti-viral medication use from the first day of onset of ILI symptoms.
- Collect a NP swab for evaluation of the presence of influenza virus following the procedures for collecting, processing and shipping as described in the Lab Manual.

- Evaluate the subject's body temperature (preferably oral), heart rate, respiratory rate and blood pressure and perform a symptom-directed physical examination.
- Record the ILI, related information, medically-attended adverse events from ILI onset and associated concomitant medication in the source documents and in the eCRF (ILI-report and adverse events section).
- Schedule in next study activity

ILI Follow-up Safety Call

An ILI follow-up safety call will be performed at 30 (+7) days after primary protocol-defined ILI onset, amongst subjects who have had their NP swab obtained

During the visit the following procedures should be carried out:

- Assess ILI symptoms and associated medication, if any.
- Assess for medically-attended adverse event.
- Remind subject of next study activity.

5.5 Study Termination Visit

The study termination visit will occur on Day 366. The termination visit must be a clinic visit; unless the subject is early terminated in which case a study termination visit may be a telephone call. The date of termination is the date of the last contact (clinic visit or telephone call) in which the subject's health status was assessed or, in cases where the subject does not agree to any further safety follow-up; it is the date consent is withdrawn. This date should be recorded on the termination eCRF page. For visit procedures to be performed for a subject whose planned study participation ends prematurely, please see Section 5.5.1, Early Termination Visit.

At the clinic visit, the following procedures will be performed:

- Interview the subject to obtain information regarding potential SAEs, ILIs, NOCDs, AEs leading to withdrawal and AESIs and the medication to treat these.
- Ask the subject as to whether he or she was hospitalized or was evaluated at an emergency room for any illness since the site's last contact with the subject. If an SAE has been identified by the site staff during the interview and has not previously been reported by the subject, this SAE must be reported by the site within 24 hours to Seqirus or delegate. Record any additional relevant medical history as needed.

  An assessment will be performed to determine if symptoms of ILI are present. Potential ILI symptoms will be documented in the subject's source records. If the onset of the ILI is 3, or at most 6, days before the visit, an NP swab should be

collected from the subject for influenza testing and study staff will document the ILI on an Adverse Event and ILI CRF. See procedures described in Section 5.4, Unscheduled Visits. Should an ILI be identified, it is recommended to postpone the study termination visit, to allow for the ILI follow-up visit to occur.

- Should the subject have experienced a protocol defined ILI for which an NP swab was obtained, please ensure collection and review of the ILI booklet and collect the information of any medically-attended adverse events which have occurred within 30 days after the onset of the of ILI.
- A qualified healthcare professional will perform a brief symptom-directed physical examination if necessary according to symptoms the subject has reported. This is a physical examination that will include an examination of organ systems that are relevant to the investigator based on review of the subject's reported adverse events, concomitant medication use. This assessment may include: measurement of vital signs (respiratory rate, blood pressure and heart rate), body temperature (preferably oral) and a check of general appearance. The physical assessment must be performed by the investigator or designee of the investigator, who is qualified to perform a physical assessment in accordance with their institutional policy. Measurement and recording of vital signs and body temperature may be conducted by a trained health care professional. Corresponding information is documented in the subject's source document and eCRF(s). Measurement and recording of vital signs and body temperature may be conducted by a trained health care professional.

The site will review with the subject or legal guardian the plan of when information relating to the subject's participation in the study may be available (e.g., study results, treatment assignments). It will also be discussed how information relating to the subject's participation in the study will be shared with the subject's healthcare provider, if the subject or legal guardian chooses to share this information.

The site will complete the termination eCRF page and this will mark the completion of the subject's participation in the study.

5.5.1 Early Termination Visit

When a subject is withdrawn from treatment or withdraws from the study, the investigator will notify the Sponsor and, when possible, will perform the procedures listed below. The reason(s) for the early termination will be included in the subject's source documentation. If the Early Termination Visit is a telephone call, collect as much information as possible.

At the clinic visit or during the telephone call, the same procedures will be performed as during the study termination visit, see Section 5.5 Study Termination Visit, if possible.

In addition, the following procedures will be performed:

- Collect and review Subject Diary, if applicable.
- Review the subject's safety data (if collection of these was in progress at the time of study termination).
- Collect and review ILI booklet, if applicable.

The site will review with the subject or legal guardian the plan of when information relating to the subject's participation in the study may be available (e.g., study results, treatment assignments). It will also be discussed how information relating to the subject's participation in the study will be shared with the subject's healthcare provider, if the subject or legal guardian chooses to share this information.

The site will complete the termination eCRF page and this will mark the completion of the subject's participation in the study.

6. TREATMENT OF SUBJECTS

All vaccines associated with this study are to be stored separately from other vaccines and medications in a secure location under appropriate storage conditions with temperature monitoring. **All vaccines associated with this study must be checked for expiration date prior to use. Expired vaccines must not be administered to subjects.**

6.1 Study Vaccine(s)

The term 'study vaccine' refers to those vaccines provided by the Sponsor, which will be evaluated as part of the study objectives. The study vaccines specific to this study are described below.

Investigational Vaccine: aQIV

An approximately 0.5 mL dose of aQIV (quadrivalent MF59C.1 adjuvanted influenza vaccine) contains nominally 15 µg of haemagglutinin (HA) of each of the 2 influenza type A strains and each of the 2 influenza type B strains for a total of 60 µg of HA in the vaccine. The strain composition will be that recommended by the WHO for quadrivalent influenza vaccines contemporaneous to the timing of the study. The full composition of the vaccine is reported in Table 6.1-1.

Table 6.1-1: aQIV Vaccine Composition

Names of Ingredients	Quantity per dose*	Function
Active Ingredients Haemagglutinin (HA) and Neuraminidase (NA) antigens from the influenza virus strains recommended by the WHO / CBER/ CHMP for the manufacture of influenza vaccine for season A/ (H1N1) A/ (H3N2) B/ (Yamagata lineage) B/ (Victoria lineage)	nominally 15µg HA/strain	Active ingredient
Adjuvant		
Squalene	9.75mg	oil phase
Polysorbate 80	1.175mg	Surfactant
Sorbitan trioleate	1.175mg	Surfactant
Sodium citrate	0.66mg	Buffer
Citric acid	0.04mg	Buffer

Names of Ingredients	Quantity per dose*	Function
Other Ingredients		
Sodium chloride	4.00mg	Isotonic aid
Potassium chloride	0.10mg	Buffer
Potassium dihydrogen phosphate	0.10mg	Buffer
Disodium phosphate dihydrate	0.67mg	Buffer
Magnesium chloride hexahydrate	0.05mg	Stabiliser
Calcium chloride dihydrate	0.06mg	Stabiliser
Water for injection	up to 0.50mL	Diluent
**		
Volume of Formulation	0.5 mL	
Appearance	Liquid, milky-white emulsion	
Vaccine Presentation	Pre-filled syringe	

* the quantities indicated in this table reflect the amount in a 0.5 mL dose.

** residues of special relevance: barium sulphate, cetyltrimethylammonium bromide (CTAB), chicken proteins, such as ovalbumin, formaldehyde, kanamycin and neomycin sulphate.

Control Vaccine: Boostrix®

Boostrix® is a combined Tetanus Toxoid, Reduced Diphtheria Toxoid and Acellular Pertussis Vaccine, Adsorbed. An approximately 0.5 mL dose of Boostrix® will be administered to the subject. The full composition of the vaccine is reported in Table 6.1-2. For a comprehensive review of Boostrix® please refer to the Summary of Products Characteristics/ Package Insert supplied by Seqirus or delegate; this document should be reviewed by the Investigators prior to initiating the study.

Table 6.1-2: Boostrix® Vaccine Composition

Names of Ingredients	Quantity per dose*
Active Ingredients	
Diphtheria toxoid	Not less than 2 International Units (IU) (2.5 Lf)
Tetanus toxoid	Not less than 20 International Units (IU) (5.0 Lf)
Bordetella pertussis antigens	
Pertussis toxoid	8 micrograms
Filamentous Heamagglutinin	8 micrograms
Pertactin	2.5 micrograms
Adjuvants	
Adsorbed on aluminium hydroxide	≤ 0.39 milligrams Al^{3+}
Other Ingredients	
Sodium chloride	4.5 milligrams
Water for injection	
Volume of Formulation	0.5 mL
Appearance	Liquid, turbid white suspension
Vaccine Presentation	Pre-filled syringe

* the quantities indicated in this table reflect the amount in a 0.5 mL dose.

** residues of special relevance: polysorbate 80 (Tween 80) and formaldehyde.

6.2 Non-Study Vaccines

The term 'non-study vaccine' refers to those vaccines which will be intentionally given to study subjects but not formally included in the analysis of study objectives. Non-study vaccines will not be provided by Seqirus.

6.3 Vaccine Preparation and Administration

The vaccine must be prepared according to the instruction sheet (aQIV) or package insert (Boostrix®) before use. Expired vaccines must not be administered.

The investigator or designee will be responsible for oversight of the administration of vaccine to subjects enrolled in the study according to the procedures stipulated in this study protocol. All vaccines will be administered only by unblinded personnel who are qualified to perform that function under applicable local laws and regulations for the specific study site.

Both vaccines are to be provided in prefilled syringes (PFS), each with an injectable volume of approximately 0.5 mL. The full volume contained in the PFS is to be administered.

Vaccination will be performed intramuscularly, preferably in the deltoid muscle of the non-dominant arm.

It is recommended that 25 gauge, 25mm (1 inch) of length needle is used for the vaccine administration.

Detailed vaccine preparation and administration instructions will be provided to investigators in the Protocol Ancillary Document prior to study start.

PRECAUTIONS TO BE OBSERVED IN ADMINISTERING STUDY VACCINE:

Prior to vaccination, subjects must be determined to be eligible for study vaccination and it must be clinically appropriate in the judgment of the investigator to vaccinate. Eligibility for study vaccine administration is determined by evaluating the entry criteria outlined in protocol Sections 4.1, Inclusion Criteria and 4.2, Exclusion Criteria.

Delay of study vaccination is determined by following the criteria outlined in Section 4.3, Criteria for Delay of Vaccination.

Study vaccines should not be administered to individuals with known hypersensitivity to any component of the vaccines.

Shake the vaccine well before use to form a homogeneous suspension. The vaccine should be visually inspected for particulate matter and discoloration prior to administration. In the event of any foreign particulate matter and/or variation of physical aspect being observed, do not administer the vaccine and contact the Sponsor and report the issue as a Pharmaceutical Technical Complaint. Do not discard the vaccine until authorized by Seqirus.

Standard vaccination practices are to be observed and care should be taken to administer the injection intramuscularly. Before administering vaccine, the vaccination site is to be disinfected with a skin disinfectant (e.g., 70% alcohol). Allow the skin to dry. **DO NOT inject intravascularly**.

As with all injectable vaccines, trained medical personnel and appropriate medical treatment should be readily available in case of anaphylactic reactions following vaccine administration. For example, epinephrine 1:1000, diphenhydramine, and/or other medications for treating anaphylaxis should be available.

6.4 Vaccine Administration Error or Overdose of Vaccine

Vaccine administration error is defined as receiving a dose of study vaccine that was not reconstituted as instructed or administered by a different route from the intended route of administration. An overdose of study vaccine (whether accidental or intentional) is defined when a dosage higher than the recommended dosage (as per the aQIV dosing regimen referred to in Table 6.1-1 or as per the package insert of Boostrix®) is administered.

Any vaccine administration error or overdose of study vaccine detailed in this protocol must be reported as an adverse event, and if the vaccine administration error or overdose is associated with a SAE, it must be reported as such within 24 hours to the Sponsor.

6.5 Prior and Concomitant Medications and Vaccines

All influenza vaccination history in the 5 years prior to subject enrolment into the study is to be obtained from the subject and recorded in the subject's source records. All influenza vaccinations received by the subject in the 12 months prior to enrolment into the study should additionally be recorded on the Prior and Concomitant Medications eCRF.

All medications and vaccines taken or received by the subject within 2 months prior to the start of the study are to be recorded on the Prior and Concomitant Medications eCRF. Any blood products received within 3 months prior to enrolment must also be documented in the Prior and Concomitant Medications eCRF. Vitamins and minerals are excluded from this scope.

In addition, the following are considered prior medications for this protocol and should be documented in the Prior and Concomitant Medications CRF: all medication/vaccines described in the inclusion and exclusion criteria (see Section 4, Selection of Study Population) of this protocol including:

- Any influenza vaccine within 1 year prior to enrolment.
- Any diphtheria or tetanus toxoid or pertussis (acellular or whole cell) vaccines within the previous 5 years.
- Systemic administration of corticosteroids (PO/IV/IM) at a dose equivalent to 20 mg of prednisone for more than 14 consecutive days within 90 days prior to informed consent.
- Administration of antineoplastic and immunomodulating agents (e.g TNFα antagonists or anti-B cell monoclonal antibodies) or radiotherapy within 1 year prior to informed consent.
- Immunoglobulins or any blood products within 180 days prior to informed consent.

- Any investigational or non-registered medicinal product within 30 days prior to informed consent.
- Any inactivated vaccines 14 days or live-attenuated vaccine 28 days prior to enrolment in this study.

The use of antipyretics and/or analgesic medications within 24 hours prior to vaccination must be identified and the reason for their use (prophylaxis versus treatment) must be described in the source document and Concomitant Medications eCRF. The use of antipyretics/analgesics within 24 hours prior to vaccine administration is a reason to delay study vaccination (see Section 4.3, Criteria for Delay of Vaccination.

The use of antipyretics and/or analgesic medications and the reason for their use (prophylaxis versus treatment) will be documented along with solicited adverse events on the Subject Diary daily until Day 7 for subjects participating in the solicited safety subset (see Section 7.1.1 Solicited Adverse Events).

Medications taken for prophylaxis are those intended to prevent the onset of symptoms. Medications taken for treatment are intended to reduce or eliminate the presence of symptoms that are present.

Concomitant medications include all medications (including vaccines) taken by/administered to the subject at and after enrolment.

The following concomitant medications will be recorded in the Concomitant Medications eCRF:

- All concomitant medications (including vaccines) from Day 1 to Day 22.
- All medications associated with SAEs, NOCD, AESIs, ILIs and AEs that lead to premature withdrawal from the study, from Visit 1 to study termination.
- All medications associated with any medically-attended adverse events within 30 days after the ILI onset

When recording concomitant medications/vaccines, they should be checked against the study entry and continuation criteria in Section 4, Selection of Study Population to ensure that the subject should be enrolled/continue in the study.

In addition, use of the following concomitant medications after enrolment should be documented on the Concomitant Medication eCRF page as they may have an effect on the interpretation of the study objectives and therefore if used, may be determined to be a reason for exclusion from one of the analysis sets.

- Anti-viral medication following ILI, prior to obtaining NP swab

- Administration of the seasonal influenza vaccines during study participation
- Blood, blood products or a parenteral immunoglobulin preparation
- Oral or systemic corticosteroids (topical, inhaled, intranasal corticosteroids are permitted)
- Other immunosuppressive agents
- Any vaccine within 28 days of study vaccination

6.6 Vaccine Supply, Labeling, Storage and Tracking

The Sponsor will ensure the following:

- Supply the study vaccine(s).
- Appropriate labeling of all study vaccines provided that complies with the legal requirements of each country where the study is to be performed.

The investigator must ensure the following:

- Acknowledge receipt of the study vaccines by a designated staff member at the site, including:
  - Confirmation that the vaccines were received in good condition
  - Confirmation to the Sponsor of the temperature range during shipment from the Sponsor to the investigator's designated storage location
  - Confirmation by the Sponsor that the vaccines are authorized for use.
- Proper storage of the study vaccines, including:
  - Storage in a secure, locked, temperature-controlled location.
  - Proper storage according to the instructions specified on the labels.
  - Appropriate record keeping and inventory of the study vaccines, including regular documentation of adequate storage temperature.
- Appropriate use of the study vaccines, including:
  - Not use of vaccines prior to receipt of authorization for use from the Sponsor.
  - Use only in accordance with the approved protocol.
  - Proper handling, including confirmation that the vaccine has not expired prior to administration.
  - Appropriate blinded documentation of administration of vaccines to study subjects including:

  - Date, dosage, batch/lot numbers, expiration dates, unique identifying numbers assigned to subjects and study vaccines, and time of vaccine administration. This information will be maintained in an accountability log that will be reviewed by the site monitor.
  - Reconciliation of all vaccines received from the Sponsor. Reconciliation is defined as maintaining records of which and how many vaccines were received, which vaccines were administered to subjects, which vaccines were destroyed at the site, and which vaccines were returned to the Sponsor, as applicable.

- Proper adherence to the local institutional policy with respect to destruction of study vaccines.
- Complete record keeping of vaccine use, wastage, return or destruction, including documentation of:
  - Copy of the site's procedure for destruction of hazardous material.
  - Number of doses destroyed, date of destruction, destruction code (if available), method of destruction, and name of individual performing destruction.

Vaccines that have been stored differently from the manufacturer's indications **must not** be used unless the Sponsor provides written authorization for use. In the event that the use cannot be authorized, the Sponsor will make every effort to replace the vaccine supply. All vaccines used in conjunction with this protocol must be stored separately from normal hospital/practice stocks to prevent unintentional use of study vaccines outside of the clinical study setting.

Monitoring of vaccine accountability will be performed by the study monitor during site visits and at the completion of the study.

At the conclusion of the study, and as appropriate during the course of the study, the investigator must ensure that all unused study vaccines, packaging and supplementary labels are destroyed locally (upon approval from Sponsor) or returned to the Sponsor.

7. ASSESSMENTS

7.1 Safety Assessment

The measures of safety used in this study are routine clinical procedures. They include a close vigilance for, and stringent reporting of, selected local and systemic adverse events routinely monitored in vaccine clinical studies as indicators of reactogenicity.

An adverse event (AE) is defined as any untoward medical occurrence in a subject or clinical investigation subject administered a pharmaceutical product at any dose that does not necessarily have to have a causal relationship with this treatment. Therefore, an AE can be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of an investigational product, whether or not considered related to the investigational product. This definition includes intercurrent illnesses or injuries and exacerbation of pre-existing conditions.

The period of observation for AEs extends from the time the subject signs informed consent until he or she completes the specified safety follow-up period Day 366 or terminates the study early (whichever comes first). AEs occurring after the ICF is signed but prior to receiving study vaccine/product will be documented as an adverse event and recorded within source document. However, any AEs occurring prior to receipt of any study vaccine will be analyzed separately from "treatment emergent" AEs (AEs occurring after administration of the first study vaccine).

Adverse events are collected as either solicited or unsolicited adverse events. Solicited events are derived from organized data collection systems, such as Subject Diaries or interview.

7.1.1 Solicited Adverse Events

The term "reactogenicity" refers to solicited signs and symptoms ("solicited adverse events") occurring in the hours and days following a vaccination, to be collected by subjects participating in the solicited safety subset subject or legal their guardian for 7 consecutive days, using a pre-defined Subject Diary.

The following solicited adverse events are included in the Subject Diary. Each adverse event is to be assessed using the scoring system reported below:

Solicited Local Adverse Events

Induration, erythema and ecchymosis will be measured by the subject and recorded directly on the Subject Diary.

Injection site pain will be measured as follows: grade 0= absent, grade 1/mild= present but does not interfere with activity, grade 2/moderate = interferes with activity, grade 3/severe = prevents daily activity.

Solicited Systemic Adverse Events

Loss of appetite will be measured as follows: grade 0 = none, grade 1/mild = eating less than usual with no effect on normal activity, grade 2/moderate = eating less than usual / interfered with normal activity, grade 3/severe = not eating at all.

Nausea will be measured as follows: grade 0 = none, grade 1/mild = no interference with daily activity, grade 2/moderate = interferes with daily activity, grade 3/severe = prevents daily activity.

Fatigue, generalized myalgia, generalized arthralgia, headache and chills will be measured using the following scoring system: grade 0 = none, grade 1/mild= no interference with daily activity, grade 2/moderate = interferes with daily activity, grade 3/severe = prevents daily activity.

Vomiting will be measured as follows: grade 0 = none, grade 1/mild = 1-2 times per 24 hours, grade 2/moderate = 3 to 5 times per 24 hours, grade 3/severe = 6 or more times in 24 hours or requires intravenous hydration.

Diarrhea will be measured as follows: grade 0 = fewer than 2 loose stools per 24 hours, grade 1/mild = 2-3 loose stools in 24 hours, grade 2/moderate = 4-5 stools in 24 hours, grade 3/severe = 6 or more loose stools in 24 hours or requires intravenous hydration.

Other Solicited Adverse Events

- Use of analgesics/antipyretics will be captured as “absent” or “present” and will also be summarized by “for treatment” or “for prophylaxis”
- Body temperature will be captured. Fever is defined as body temperature ≥38.0 ◦C, as measured preferably orally

For subjects participating in the solicited safety subset, the study staff must review the data entered into the Subject Diary as described in Section 3.4.2, Tools Used for Data Collection and section 5.3.1, Follow-up Clinic Visit(s).

Note: Any solicited adverse event that meets any of the following criteria must be entered into subjects’ source document (see Section 9.1, Source Documentation) and also as an adverse event on the Adverse Event CRF:

- Solicited local or systemic adverse event that continues beyond Day 7 after vaccination.
- Solicited local or systemic adverse event that leads to a visit to a healthcare provider (medically attended adverse event, see Section 7.1.3, Evaluation of Adverse Events).
- Solicited local or systemic adverse event leading to the subject withdrawing from the study or the subject being withdrawn from the study by the investigator (adverse event leading to withdrawal, see Section 7.1.3, Evaluation of Adverse Events).
- Solicited local or systemic adverse event that otherwise meets the definition of a SAE (see Section 7.1.4, Serious Adverse Events).

7.1.2 Unsolicited Adverse Events

An unsolicited adverse event is an adverse event that was not solicited using a Subject Diary and that was spontaneously communicated by a subject or legal guardian who has signed the informed consent.

Potential unsolicited AEs may be medically attended (defined as symptoms or illnesses requiring hospitalization, or emergency room visit, or visit to/by a health care provider – refer to CRF Instructions for further guidance), or were of concern to the subject or legal guardian(s). In case of such events, subjects or legal guardian(s) will be instructed to contact the site as soon as possible to report the event(s). The detailed information about the reported unsolicited AEs will be collected by the qualified site personnel during the interview and will be documented in the subject's records.

Unsolicited AEs that are not medically attended nor perceived as a concern by subjects or legal guardian(s) will be collected during interview with the subject or legal guardian(s) and by review of available medical records at the next visit (see section 5.3, Post-vaccination Visit(s)).

7.1.3 Evaluation of Adverse Events

Every effort should be made by the investigator to evaluate safety information reported by a subject for an underlying diagnosis and to capture this diagnosis as the event in the AE page. In other words, the practice of reporting only symptoms (e.g., "cough" or "ear pain") are better reported according to the underlying cause (e.g., "asthma exacerbation" or "otitis media").

The severity of events reported on the Adverse Events CRF will be determined by the investigator as:

Mild: transient with no limitation in normal daily activity.
Moderate: some limitation in normal daily activity.
Severe: unable to perform normal daily activity.

The relationship of the study treatment to an AE will be determined by the investigator based on the following definitions:

1. Not Related

The AE is not related to an investigational vaccine if there is evidence that clearly indicates an alternative explanation. If the subject has not received the vaccine, the timing of the exposure to the vaccine and the onset of the AE are not reasonably related in time, or other facts, evidence or arguments exist that reasonably suggest an alternative explanation, then the AE is not related.

2. Possibly Related

The administration of the investigational vaccine and AE are considered reasonably related in time and the AE could be explained by exposure to the investigational vaccine or by other causes.

3. Probably Related

Exposure to the investigational vaccine and AE are reasonably related in time and no alternative explanation has been identified.

The relationship of the study treatment to an unsolicited AE will be determined by the investigator.

Note: solicited AEs will not be evaluated for relationship to study treatment. Grading for severity of solicited local and systemic AEs is described in Section 7.1.1, Solicited Adverse Events.

Adverse events will also be evaluated by the investigator for the co-existence of any of the other following conditions:

- AESI see Section 7.1.4.1, AESI.
- "New onset of chronic disease" (NOCD): an adverse event that represents a new diagnosis of a chronic medical condition that was not present or suspected in a subject prior to study enrolment.
- AEs leading to withdrawal: adverse events leading to study or vaccine withdrawal.

If solicited or unsolicited adverse events have been reported and the subject or legal guardian(s) indicated that the symptoms required medical attendance or were of concern, the subject or legal guardian(s) must be contacted for further information.

When the subject or legal guardian(s) is contacted for any of these reasons, the contact must be documented in the subject's source documentation.

All AEs, regardless of severity, will be monitored until resolution or until the investigator assesses them as chronic or stable. All subjects experiencing AEs - whether considered associated with the use of the study vaccine or not - must be monitored until symptoms subside and any abnormal laboratory values have returned to baseline, or until there is a satisfactory explanation for the changes observed, or until death, in which case a full pathologist's report should be supplied, if possible. The investigator's assessment of ongoing Adverse Events at the time of each subject's last visit should be documented in the subject's medical chart.

7.1.4 Serious Adverse Events

A SAE is defined as any untoward medical occurrence that at any dose results in one or more of the following:

- Death.
- Is life-threatening (i.e., the subject was, in the opinion of the investigator, at immediate risk of death from the event as it occurred); it does not refer to an event which hypothetically might have caused death if it were more severe.
- Required or prolonged hospitalization.
- Persistent or significant disability/incapacity (i.e., the event causes a substantial disruption of a person's ability to conduct normal life functions).
- Congenital anomaly/or birth defect.
- An important and significant medical event that may not be immediately life threatening or resulting in death or hospitalization but, based upon appropriate medical judgment, may jeopardize the subject or may require intervention to prevent one of the other outcomes listed above.

Adverse events which do not fall into these categories are defined as non-serious.

It should be noted that a severe adverse event need not be serious in nature and that a SAE need not, by definition, be severe.

Serious adverse events will be captured both on the Vaccines Serious Adverse Event (VSAE) form as well as on the AE CRF. All SAEs will be evaluated by the investigator for relationship of the event to study vaccine. SAEs that are judged to be possibly or probably related to the study vaccine should be reported to the Sponsor as related/suspected events.

The relationship of the study treatment to an SAE will be determined by the investigator based on the following definitions:

1. Related/suspected

The SAE is judged by the investigator to be possibly or probably related to the study vaccine on the AE CRF page (see Section 7.1.3, Evaluation of Adverse Events).

2. Not Related

The SAE is not related if exposure to the study vaccine has not occurred, **or** the occurrence of the SAE is not reasonably related in time, **or** the SAE is considered unlikely to be related to use of the study vaccine, i.e., there are no facts (evidence) or arguments to suggest a causal relationship.

The relationship of the study vaccine to an SAE will be determined by the investigator.

In addition, SAEs will be evaluated by the Sponsor or designee for "expectedness." An unexpected AE is one that is not listed in the current Summary of Product Characteristics or the Investigator's Brochure or an event that is by nature more specific or more severe than a listed event.

In addition, a pre-existing event or condition that results in hospitalization should be recorded on the Medical History CRF. If the onset of an event occurred before the subject entered the study (e.g., any pre-planned hospitalization for conditions like cosmetic treatments or for non-emergency routine visits for a pre-existing condition), the hospitalization would not lead to an AE being classified as serious unless, in the view of the investigator, hospitalization was prolonged as a result of participation in the clinical study or was necessary due to a worsening of the pre-existing condition.

7.1.4.1 Adverse Events of Special Interest

The investigator will be provided with a list of AESIs prior to FSFV. Receipt of this list will be documented and stored, along with the list of AESIs in the Investigator Study File. During the course of the trial the list of AESI may change. If this occurs the investigators will be advised of the change and confirmation of receipt will be documented. The

updated list of AESIs and documentation of receipt are also stored in the Investigator Study File.

Subjects will be assessed at each visit for any new medical events or signs or symptoms that could possibly indicate an AESI. The subject will be asked whether any new diagnosis has been given to the subject through a review of recent medical history. Should a qualified health care practitioner who is not the investigator suspect a potential AESI, she/he should promptly inform the investigator. The AESI diagnosis will be recorded in the medical chart/source document as well as in the Adverse Events CRF along with any medication used to treat the condition.

A diagnosis of an AESI is to be reported in the same manner and time frame as an SAE using the VSAE form. The investigator must notify Seqirus within 24hrs. The AESI diagnosis as well as any medication taken to treat the condition, will be recorded in the subject's source documents and on the Adverse Events eCRF.

7.1.5 Methods for Recording Adverse Events and Serious Adverse Events

Findings regarding Adverse Events must be reported on an Adverse Events CRF, as specified in Section 7.1.1, Solicited Adverse Events, and on the VSAE form, if applicable, which is part of the Investigator Site File. All findings in subjects experiencing AEs must be reported also in the subject's source document.

All SAEs which occur during the course of the study, whether considered to be associated with the study vaccination or not, must be reported **within 24 hours of the site becoming aware of the event** to Seqirus or its designee. Specific instructions and contact details for collecting and reporting SAEs to Seqirus or delegate will be provided to the investigator.

All SAEs are also to be documented on the Adverse Events CRF. Any medication or other therapeutic measures used to treat the AE will be recorded on the appropriate CRF(s) in addition to the outcome of the AE.

After receipt of the initial report, representatives of Seqirus or its designee will contact the investigator if it is necessary to obtain further information for assessment of the event.

All SAEs must be reported by the investigator to his/her corresponding EC/IRB or applicable regulatory authorities in accordance with institutional policy/regulatory requirements and adequate documentation of this notification must be provided to the Sponsor.

Seqirus or its designee must also comply with the applicable regulatory requirement(s) related to the reporting of suspected unexpected serious adverse vaccine reactions (also

known as SUSARs) to the regulatory authority (ies) and the IRB/EC. If a SUSAR or other safety signal relating to use of one of the study vaccines is reported to Seqirus or its designee, the Sponsor will communicate the information to the investigator and the investigator will be responsible for submitting this information to the EC/IRB and other relevant authorities.

7.1.5.1 Post-Study Events

Any SAE that occurs outside of the protocol-specified follow-up period and considered to be caused by the study vaccine must be reported to Seqirus or its designee. These SAEs will be processed by Seqirus or its designee as during the course of the study, until 6 months afterwards. Instructions and contact details for collecting and reporting these suspected SAEs will be provided to the investigator.

7.1.6 Pregnancies

Not applicable for this study.

7.1.7 Safety Laboratory Measurements

No scheduled safety laboratory measurements are planned for this study.

7.2 Efficacy Assessment

Confirmation of influenza infection by RT-PCR or culture from a nasopharyngeal swab sample is necessary for the efficacy assessment in the study. Nasopharyngeal swab retrieval will be initiated after primary protocol-defined ILI has been identified. Primary protocol-defined ILI can occur at any time during the study and will be evaluated in each subject from Visit 1 (Day 1) through Study Termination. ILI symptoms will be captured during study visits. The ILI onset day is defined as the first day that the subject meets the primary protocol-defined ILI. The end date is defined as the date the last symptom resolves. A new ILI episode will only be taken into account after resolution of the previous one, as judged by the investigator (suggested interval between two ILI episodes is 14 symptom-free days).

Subjects with primary protocol defined ILI will have a NP swab collected for evaluation of the presence of influenza virus. NP swabs should be targeted for collection within 3 days from the ILI onset to ensure optimal viral yield, however samples will be accepted if collected up to 6 days following the day of ILI onset. NP swabs will not be taken beyond a total of 7 days (6 days following onset of ILI) as the level of virus detectable beyond this period can be negligible, particularly for influenza A.

All NP swabs collected from subjects with ILI will be shipped under pre-specified conditions in viral transport media to a qualified lab and stored for analysis for influenza.

NP swabs will be analyzed by RT-PCR and placed into culture. The result of the RT-PCR assay will be the presence or absence of influenza virus. The viral culture will be used for the purpose of viral expansion to enable phenotypic characterization of the influenza virus (e.g. antigenic match). Testing will be conducted by a designated laboratory in a blinded manner towards the treatment arm. Please see the Protocol Ancillary Document for name(s) and details.

7.3 Immunogenicity Assessment

The measures of immunogenicity used in this study are standard, i.e., widely used and generally recognized as reliable, accurate, and relevant (able to describe the quality and extent of the immune response).

The secondary immunogenicity analysis will evaluate immunogenicity of aQIV measured by the HI assay by titrating antibodies against the influenza strains homologous to the seasonal vaccine (see Section 2.2, Secondary Objectives). Additional immunologic assays, including microneutralization, may be used to measure neutralizing antibodies and to facilitate exploration and estimation of an immune correlate of protection.

The time points for the evaluation of antibody responses after vaccination will help to inform how a subject responds to the aQIV vaccine compared to the non-influenza comparator vaccine at Day 1 (baseline) and 22 for HI Peak antibody responses to the strains selected for the seasonal vaccine are typically observed after 3 weeks of vaccination.

Testing will be conducted by a Seqirus or designated laboratory in a blinded manner towards the treatment arm and the visit. Please see the Protocol Ancillary Document for name(s) and details.

8. STATISTICAL CONSIDERATIONS

8.1 Endpoints

8.1.1 Primary Endpoint(s)

8.1.1.1 Primary Safety Endpoint(s)

Safety objective 2 will be assessed by calculating the percentage of subjects in the solicited safety subset with solicited local and systemic adverse events from Day 1 through Day 7. Solicited local and systemic adverse event data from Day1-7 will be obtained from data collected on subject diary cards. Only subjects randomly selected for participation in the solicited safety subset will be asked to fill out subject diary cards from Day 1-7. Safety objectives 3 and 4 will be assessed based on:

- Percentage of subjects with medically-attended adverse events within 30 days after of first occurrence RT-PCR confirmed ILI.
- percentages of subjects with any unsolicited AEs and concomitant medications reported from Day 1 through Day 22;
- percentages of subjects with SAEs, AEs leading to withdrawal from the study, NOCD, AESI reported from Day 1 to Day 366 and all concomitant medications associated with these events.

8.1.1.2 Primary Efficacy Endpoint(s)

The primary efficacy endpoint is the time to first-occurrence of RT-PCR-confirmed influenza from 21 through 180 days after vaccination or end of the influenza season, whichever is longer.

The end of the influenza season will be defined as the end of June for Northern Hemisphere (NH) influenza season and end of December for Southern Hemisphere (SH) influenza season. For tropical countries, with no typical NH or SH influenza season, the season is defined by the use of the strains in the vaccine formulation (i.e. strains as recommended for the NH or the SH influenza season) and the timing of vaccination.

An influenza event is defined as RT-PCR- or culture-confirmed influenza infection in the setting of an influenza-like illness (ILI). The primary protocol-definition of ILI will be used to define success for the primary and key secondary efficacy endpoint.

8.1.1.3 Primary Immunogenicity Endpoint(s)

There are no primary immunogenicity endpoints in this study.

8.1.2 Secondary Endpoint(s)

8.1.2.1 Secondary Safety Endpoint(s)

There are no secondary safety endpoints in this study.

8.1.2.2 Secondary Efficacy Endpoint(s)

Additional efficacy endpoints are sought based on antigenic match of culture isolated influenza to the strains of virus contained in the seasonal vaccine. Both definitions of ILI will be used to determine the efficacy endpoints

Vaccine efficacy will be determined based on either:

- Antigenically matched strains of influenza virus (Secondary Efficacy Objective 1).
- Influenza strains regardless of antigenic match (Secondary Efficacy Objective 2 and 4)
- Antigenically unmatched strains of influenza (Secondary Efficacy Objective 3).

8.1.2.3 Secondary Immunogenicity Endpoint(s)

The measures of immunogenicity used for Objective 5 as determined by the HI assay against homologous strains at Days 1 and 22, include the following:

- Geometric mean HI titers (GMT);
- GMT ratios (GMRs) at Day 22/Day 1;
- Percentages of subjects with an HI titer ≥1:40;[6]
- Percentages of subjects achieving seroconversion (defined as: HI ≥1:40 for subjects sero-negative at baseline [HI titer <1:10]; or a minimum 4-fold increase in HI titer for subjects sero-positive at baseline [HI titer ≥1:10]) on Day 22;[1]

[6] The endpoints of percent of subjects achieving seroconversion and HI titer ≥ 1:40 at Day 22 will be assessed against the criteria described in CBER Guidance Clinical Data Needed to Support the Licensure of Seasonal Inactivated Influenza Vaccines (2007). Specifically, this will be that:

- the lower bound of the two-sided 95% CI for the percent of subjects achieving seroconversion for HI antibody should meet or exceed 30%
- the lower bound of the two-sided 95% CI for the percent of subjects achieving an HI antibody titer ≥ 1:40 should meet or exceed 60%.

- Reverse cumulative distributions of HI titers at Day 22.

8.1.3 Exploratory Endpoint(s)

8.1.3.1 Exploratory Safety Endpoint(s)

There are no exploratory safety endpoints in this study.

8.1.3.2 Exploratory Efficacy Endpoint(s)

There are no exploratory efficacy endpoints in this study.

8.1.3.3 Exploratory Immunogenicity Endpoint(s)

The exploratory endpoints determined by the MN assay against homologous strains at Days 1 and 22, include the following:

- Geometric mean titer (GMT).
- Geometric mean ratio calculated at Day 22/Day 1.
- Percentage of subjects with a four-fold rise in MN antibody titer at Day 22
- Reverse cumulative distributions of MN titers at Day 22.
- Additionally, an estimate of the serologic correlate of protection on the basis of HI or other immunological responses including MN, measured three weeks after vaccination against the respective strain.

Further details regarding the statistical approach to estimate potential immunologic correlates of protection are further described in section 8.4.4.3.

8.2 Success Criteria

The study is considered successful if the primary efficacy objective is achieved together with an acceptable safety profile for aQIV vaccine.

8.2.1 Success Criteria for Primary Objective(s)

8.2.1.1 Success Criteria for Primary Safety Objective(s)

Not applicable.

8.2.1.2 Success Criteria for Primary Efficacy Objective(s)

The primary efficacy objective is achieved if the lower-limit (LL) of the two-sided 95% CI of absolute vaccine efficacy estimate is > 0.4 using the primary protocol definition of ILI. In case more than one interim analysis is necessary the type 1 error (alpha) and hence the confidence level of the interval will be adjusted.

8.2.1.3 Success Criteria for Primary Immunogenicity Objective(s)

Not applicable.

8.2.2 Success Criteria for Secondary Objective(s)

8.2.2.1 Success Criteria for Secondary Safety Objective(s)

Not applicable.

8.2.2.2 Success Criteria for Secondary Efficacy Objective(s)

The key secondary objective is achieved if the lower-limit (LL) of the two-sided 95% CI of absolute vaccine efficacy estimate is > 0.4. As for the primary efficacy objective, the CI confidence level will be adjusted to reflect adjustment of type 1 error (alpha) in case of more than one interim analysis.

Other secondary efficacy/effectiveness objectives will not be tested for success.

8.2.2.3 Success Criteria for Secondary Immunogenicity Objective

The endpoints of percent of subjects achieving seroconversion and HI titer ≥ 1:40 at Day 22 will be assessed against the criteria described in CBER Guidance Clinical Data Needed to Support the Licensure of Seasonal Inactivated Influenza Vaccines (2007):

- The lower bound of the two-sided 95% CI for the percentage of subjects achieving seroconversion for HI antibody should meet or exceed 30%.
- The lower bound of the two-sided 95% CI for the percentage of subjects achieving an HI antibody titer ≥1:40 should meet or exceed 60%.

8.3 Analysis Sets

8.3.1 All Enrolled Set

All screened subjects who provide informed consent, received subject ID and provided demographic and/or baseline screening assessments, regardless of the subject's randomization and treatment status in the study.

8.3.2 All Exposed Set

All subjects in the enrolled set who receive a study vaccination.

8.3.3 Safety Set

Solicited Safety Set (solicited local and systemic adverse events and other solicited adverse events)

A randomly selected sample of 1053 subjects from each treatment arm of the Exposed Set with any solicited adverse event data, indicating the occurrence or lack of occurrence of solicited adverse events (e.g., use of analgesics/antipyretics medication).

Unsolicited Safety Set (unsolicited adverse events)

All subjects in the Exposed Set with unsolicited adverse event data, indicating the occurrence or lack of occurrence of an adverse event.

Overall Safety Set

All subjects who are in the Solicited Safety Set and/or Unsolicited Safety Set.

Subjects will be analyzed as "treated" (i.e., according to the vaccine a subject received, rather than the vaccine to which the subject may have been randomized).

Subjects with reportable stratification errors will be analyzed "as corrected", (i.e. analyze subject in corrected stratum) in safety. Subjects with non-reportable stratification errors will be shifted and analyzed in their correct stratum in safety.

8.3.4 Full Analysis Set (FAS) Efficacy/Immunogenicity Set

Full Analysis Set Efficacy (primary and secondary efficacy objectives)

All subjects in the All Enrolled Set who are randomized and receive a study vaccination, are under observation for at least 21 days post-vaccination and provide efficacy data.

Full Analysis Set Immunogenicity

A randomly selected sample of 1,702 subjects including subjects from both treatment arms (1,362 aQIV; 340 Boostrix), in the All Enroled Set who are randomized, receive a study vaccination and provide blood specimens before and after vaccination. Several FASs for all relevant immunogenicity endpoints will be detailed in the SAP.

8.3.5 Per Protocol (PP) Set Efficacy/Immunogenicity Set

All subjects in the FAS Efficacy / Immunogenicity who:

- Correctly receive the vaccine (i.e., receive the vaccine to which the subjects is randomized and at the scheduled time points).
- Have no protocol deviations leading to exclusion (see Section 8.3.7, Protocol Deviations) as defined prior to unblinding / analysis.
- Are not excluded due to other reasons defined prior to unblinding or analysis (see Section 8.3.7, Protocol Deviations).

PPS are subsets of FAS and should be always defined even if the objectives do not require it.

Examples for subjects excluded due to other reasons than protocol deviations are subjects who withdrew informed consent.

In case of misrandomization with regard to treatment arm, the subject is excluded from the PPS. If a subject receives a vaccine, labelled for another subject but the same as the one the subject was randomized to, the subject will not be removed from the PPS.

If a subject received the correct study vaccine (dose, batch) but from another ongoing study at the site then the subject should be excluded from the PPS.

Subjects with reportable stratification error will be excluded from the PPS. A stratification error is considered “reportable” when it has a major impact to the vaccination dose and/or to the vaccination schedule of a subject.

Subjects with non-reportable stratification errors will be analyzed in the correct stratum in PPS.

If a subject is unblinded during the study, except for SUSAR, or AESI he/she will be excluded from the PPS.

8.3.6 Subgroups

The primary efficacy analysis will be performed by stratifying for the following subgroups:

- Age at enrolment (≥65-74, ≥75-84, and ≥85 years);
- Comorbidity/risk (yes/no defined as assessment score < 50 or ≥50 based on scale described in the Section 5.1.2) (Hak, 2004);
- Previous influenza vaccination in the past 5 years (yes/no);
- Smoking status (yes/no);
- Sex;
- Race;
- Country;
- By season, if applicable.

Immunogenicity analysis at Day 22 will be performed by stratifying for the following subgroups:

- Age at enrolment (≥65-74, ≥75-84, and ≥85years);
- Comorbidity/risk (yes/no defined as assessment score < 50 or ≥50 based on scale described in the Section 5.1.2) (Hak, 2004);
- Previous influenza vaccination in the past 5 years (yes/no);
- Sex;
- Race;

Safety analysis of any unsolicited adverse events and of any local, any systemic, or any other solicited adverse events (all adverse events combined for each such category) will be performed by stratifying for the following subgroups:

- Age at enrolment (≥65-74, ≥75-84, and ≥85years);
- Sex;
- Race;
- Country

8.3.7 Protocol Deviations

A protocol deviation is any change, divergence, or departure from the study design or procedures of a study protocol. A protocol deviation may be a reason to remove data from an analysis set at the time of analysis. CSR-reportable protocol deviations as well as exclusion actions taken will be specified in the SAP. In some cases exclusion of data may be due to a reason other than a protocol deviation, e.g. early termination.

8.4 Statistical Analysis Plan

8.4.1 Analysis of Demographic and Baseline Characteristics

Descriptive statistics (mean, standard deviation, median, minimum and maximum) for age, height, weight, BMI and comorbidity score at enrolment will be calculated overall and by vaccine group.

Distributions of subjects by sex, age, ethnic origin (race, ethnicity), previous vaccination status, smoking status, comorbidity and risk of complications from influenza will be summarized overall, by vaccine group, and by age group and vaccine group.

8.4.2 Analysis of Primary Objective(s)

8.4.2.1 Analysis of Primary Safety Objective(s)

8.4.2.1.1 Analysis of Extent of Exposure

The number of subjects actually receiving the vaccination will be summarized by vaccine group.

8.4.2.1.2 Analysis of Solicited Local, Systemic and Other Adverse Events

Solicited local AEs include: injection site erythema, induration, ecchymosis and pain.

Solicited systemic AEs include: loss of appetite, nausea, fatigue, generalized myalgia, generalized arthralgia, headache, chills, vomiting, diarrhea.

All solicited adverse events will be summarized according to defined severity grading scales.

Frequencies and percentages of subjects experiencing each adverse event will be presented for each symptom severity. Summary tables showing the occurrence of any local or systemic adverse event overall and at each time point will also be presented.

Post-vaccination solicited adverse events reported from day 1 to Day 7 will be summarized for the intervals Day 1-3, Day 4-7, Day 1-7 by maximal severity and by vaccine group, excluding the 30 minute measurement, which will be summarized separately. Injection-site erythema, ecchymosis and induration will be summarized according to categories based on linear measurements, please refer to the SAP for definition of categories.

Injection site pain and systemic adverse events (except fever) occurring up to 7 days after each vaccination will be summarized according to "mild", "moderate" or "severe" categorization. For the definition of severity grades please refer to the Section 7.1.1 of the protocol.

Each solicited local and systemic adverse event will also be further summarized as "none" versus "any". "Any" will include reactions with a diameter of at least 1 mm.

Implausible measurements (for further definition see SAP) will be left out of the analysis.

Use of antipyretics and analgesics will be summarized by frequency and percentage of subjects reporting use. Summaries by type of use (prophylactic versus treatment) and by treatment arm will be provided.

Body temperature will be summarized by 0.5 °C and 1.0 °C increments from 36.0 °C up to ≥40 °C and will be broken down according to route of measurement. In addition, fever will be summarized according to "mild", "moderate" or "severe" categorization. For the definition of severity grades please refer to the SAP.

8.4.2.1.3 Analysis of Unsolicited Adverse Events

This analysis applies to all adverse events occurring during the study, judged either as probably related, possibly related, or not related to vaccination by the investigator, recorded in AE CRF, with a start date on or after the date of first vaccination. AE starting prior to the first vaccination will only be listed. The original verbatim terms used by investigators to identify adverse events in the CRFs will be mapped to preferred terms using the Medical Dictionary for Regulatory Activities (MedDRA) dictionary. The adverse events will then be grouped by MedDRA preferred terms into frequency tables according to system organ class (SOC).

All reported adverse events, as well as adverse events judged by the investigator as at least possibly related to study vaccine, will be summarized according to SOC and preferred term within SOC. These summaries will be presented by vaccination group and by interval of study observation. When an adverse event occurs more than once for a

subject, the maximal severity and strongest relationship to the vaccine group will be counted.

Separate summaries will be produced for the following categories:

- SAE;
- Adverse events that are possibly or probably related to vaccine;
- Medically attended adverse events that occur within 30 days following RT-PCR confirmed ILI
- AESI;
- NOCD;
- Adverse event leading to withdrawal;
- Adverse event resulting in death.

Data listings of all adverse events will be provided by subject. In addition, adverse events in the categories above will be provided as listed data.

For **handling of missing data** the entire study period will be divided into disjoint intervals based upon the time and event schedule in the protocol:

Solicited AEs: 30 min, 6h-Day 3, Day 4-Day 7, and one overall interval: 6h-Day 7.

Unsolicited AEs: [Day 1-22], [Day 23-181], [Day 182-366], and [Day 1-366].

No imputation of missing solicited or unsolicited AEs will be used. The percentage of subjects with missing solicited AE assessments (e.g. missing Patient Diary) and missing Safety Phone Call or safety assessment will be reported for each time period.

8.4.2.1.4 Analysis of Safety Laboratory Values

Not applicable.

8.4.2.2 Analysis of Primary Efficacy Objective(s)

8.4.2.2.1 Statistical Hypotheses

The primary absolute efficacy objective will be evaluated using following null (H_0) and alternative (H_1) hypotheses:

$$H_0: 1- HR = VE \leq 0.4 \qquad \text{versus} \qquad H_1: VE > 0.4,$$

where HR is a hazard ratio of aQIV versus non-influenza comparator.

8.4.2.2.2 Analysis Sets

Primary vaccine efficacy analyses will be based on the Efficacy FAS, and repeated on the Efficacy PPS.

8.4.2.2.3 Statistical Methods

Cox Proportional Hazards (PH) model will be used to estimate the hazard ratio:

$$HR = \lambda_{aQIV}(t)/\ \lambda_{Comp}(t) = \exp(\beta_g\ (\ x_{ig}\text{-}x_{jg}) + \beta_a\ (\ x_{ia}\text{-}x_{ja}) + \beta_c\ (\ x_{ic}\text{-}x_{jc})),$$

where $\lambda_{aQIV(s)}(t)$ and $\lambda_{Comp(s)}(t)$ are stratum-specific hazards at time t, for stratum s that reflects a combination of age group (<75 vs ≥ 75 years) and low vs high (score <50 vs ≥ 50) risk of influenza complications, in aQIV and comparator group, respectively; β_g denotes regression coefficient and $x_{ig(s)}$, $x_{jg(s)}$ are indicators of treatment group for individuals i and j within stratum Subjects that did not experience ILI during observation period and subjects that dropped out from the study during observational period will be censored (right-censoring). The estimate of the hazard ratio, the respective estimate for absolute VE and pertaining 2-sided 95% CIs will be calculated based on this model. If the study continues over several seasons, estimates will be also adjusted for the factor season (s). Factor site/center or country might be added to the model if appropriate. In case of more than one interim analysis confidence level for the estimates at the final stage will be adjusted.

Estimates for hazard ratio in the PH model will be calculated using Maximum Partial Likelihood (MPL) method. In case of problems with convergence (algorithm does not converge or converges to infinite estimates) penalized ML approach will be used (Heinze and Schemper, 2001).

In case interim analyses will be performed a k-stages group - sequential test procedure for time-to-event data will be implemented. As the K-stage interim analysis for relative vaccine efficacy introduces a multiple test problem, alpha will be adjusted using error-spending function as described in Section 8.6. For this group sequential test procedure parameters like information level and/or standard error at each stage will be calculated by the above described model and then used to calculate the actual group sequential test that compared the test statistic at each stage with the respective boundaries. Repeated CIs for each stage and also the final estimator and the respective CI can be retrieved by the group sequential test method to maintain simultaneous coverage probability (Jennison, 2000).

Further details of the statistical methods will be provided in the SAP.

Missing immunogenicity values are considered missing completely at random (MCAR) and therefore will not contain information that impact the result of the analysis (i.e., not informative). Imputation methods will therefore not be used. The secondary objectives will be analyzed using the FAS (immunogenicity). If the percentage of vaccinated subject excluded from the FAS (immunogenicity) is greater than 5%, a secondary analysis based on the PPS will be performed to complement the FAS.

Efficacy data will be analyzed using both the FAS (Efficacy) and the PPS, irrespective of the difference in size between the two analysis sets.

The following algorithm will be applied:

1. If less than 20% of subjects are without efficacy data (e.g., ILI swabs collected without any RT-PCR assessment record), then the analyses will be run on FAS and PPS and no further statistical evaluation will be performed.

2. If observations are missing for 20% or more of subjects, the missing mechanism will be analyzed with vaccine group as a categorical variable and a newly created variable describing the missing information as dependent variable (1=efficacy record present; 0=efficacy record not present). It will be tested, by chi-square test, if the proportion of missing observations/subjects varies significantly between vaccine groups. If the difference is significant with $P<0.05$ then a sensitivity analysis will be performed of the primary efficacy analysis imputing randomly x% (from 0% to 100% in 10% increments) of missing data as PCR-confirmed cases.

8.4.2.3 Analysis Of Primary Immunogenicity Objective(S)

There are no primary immunogenicity objectives in this study.

8.4.2.3.1 Statistical Hypotheses

Not applicable.

8.4.2.3.2 Analysis Sets

Not applicable.

8.4.2.3.3 Statistical Methods

Not applicable.

8.4.3 Analysis of Secondary Objective(s)

8.4.3.1 Analysis of Secondary Safety Objective(s)

There are no secondary safety objectives in this study.

8.4.3.1.1 Analysis of Extent of Exposure

Not applicable.

8.4.3.1.2 Analysis of Solicited Local, Systemic and Other Adverse Events

Not applicable.

8.4.3.1.3 Analysis of Unsolicited Adverse Events

Not applicable.

8.4.3.1.4 Statistical Hypotheses

Not applicable.

8.4.3.1.5 Analysis Sets

Not applicable.

8.4.3.1.6 Statistical Methods

Not applicable.

8.4.3.2 Analysis of Secondary Efficacy Objective(s)

8.4.3.2.1 Statistical Hypotheses

Hypotheses for testing key secondary objective are formulated in the similar way as for the primary efficacy objective. Other secondary efficacy objectives are not associated with any hypothesis testing.

8.4.3.2.2 Analysis Sets

All secondary efficacy objectives will be evaluated based on the Efficacy FAS, and analysis for the key secondary objective will be also repeated based on Efficacy PPS.

8.4.3.2.3 Statistical Methods

Similarly to the primary efficacy objectives, the PH model will be used to estimate absolute vaccine efficacy for secondary objectives 1-4. Evaluation of the key secondary objective will be done according to the conditional testing procedure. Absolute efficacy of aQIV with respect to the culture confirmed matched influenza will be demonstrated only providing successful demonstration of the primary objective (absolute efficacy with respect to RT-PCR-confirmed influenza regardless of antigenic match). This conditioning allows testing of both primary and key secondary efficacy objectives on the same significance level alpha.

8.4.3.3 Analysis of Secondary Immunogenicity Objective(s)

8.4.3.3.1 Statistical Hypotheses

No statistical testing will be performed for the comparative secondary immunogenicity objectives.

CBER requirements for the aQIV vaccine group translate into following hypothesis:

$$H_{0k}^{(SC)}: \pi_{ik} - \pi_0 \leq 0 \quad \text{vs.} \quad H_{1k}^{(SC)}: \pi_{ik} - \pi_0 > 0$$

$$H_{0k}^{(SP)}: \tau_{ik} - \tau_0 \leq 0 \quad \text{vs.} \quad H_{1k}^{(SP)}: \tau_{ik} - \tau_0 > 0,$$

assuming that responses Y_{ij}, Z_{ij} are independent identically distributed Bernoulli variables $B(1, \pi_{ik})$ and $B(1, \tau_{ik})$, where i denotes vaccine group; $j=1,..,n_i$ denotes subject, k denotes strain, π_{ik} and τ_{ik} represent the population proportions of subjects achieving seroconversion and post-vaccination HI titer $\geq$ 1:40, respectively, π_0 and τ_0 denote the thresholds for seroconversion ($\pi_0 = 0.3$) and the threshold for proportion of subjects with HI titer $\geq$ 1:40 ($\tau_0 = 0.6$).

All hypothesis related to CBER criteria will be tested on unadjusted 5% significance level.

8.4.3.3.2 Analysis Sets

Secondary immunogenicity objectives will be evaluated based on the FAS.

8.4.3.3.3 Statistical Methods

All statistical analyses for HI titers will be performed on the logarithmically (base 10) transformed values. Individual HI titers below detection limit (<10) will be set to half of that limit (5).

Crude estimates for GMTs, GMRs and pertaining 2-sided 95% CIs will be calculated assuming log-normal distribution of the titers and will be completed by providing minimum, maximum and median titers for each vaccine group.

Binary data (i.e., percentages of subjects with seroconversion and with titer ≥ 1:40) will be summarized for each group using crude estimates and will be reported together with 2-sided 95% CIs calculated according to Clopper's and Pearson's (1934) method. No multiplicity adjustment to the CI levels will be implemented.

For immunogenicity data, it may be reasonable to consider missing immunogenicity values as missing completely at random (MCAR), i.e., not informative. Therefore, the key secondary analysis will comprise a complete case analysis only, without introducing any bias. Imputation methods will not be used.

8.4.4 Analysis of Exploratory Objectives

8.4.4.1 Analysis of Exploratory Safety Objective(s)

There are no exploratory safety objectives in this study.

8.4.4.2 Analysis of Exploratory Efficacy Objective(s)

There are no exploratory efficacy objectives in this study.

8.4.4.3 Analysis of Exploratory Immunogenicity Objective(s)

Exploratory objectives related to the MN-assay will be evaluated using methods for lognormal and binomial data as described in the Section 8.4.3.3.3.

Evaluation of a Serological Predictor of Protection Against Influenza

The immunogenicity data of the blood draw 21 days after vaccination from all subjects reporting an influenza case and subjects randomized from the population without an influenza case serving as the control group will be used to evaluate the relationship between antibody levels tested with the HI assay and clinical protection from influenza.

The Prentice criterion will be used to assess, whether an immunologic correlate of protection can be determined.

To accommodate the criterion a linear logistic regression model will be fitted with vaccine group included as independent predictor and incidence of influenza as dependent variable to show that the observed vaccine effect be explained in a statistical model using immunologic data.

A second logistic regression model will be fitted, adjusted for log-transformed antibody titer and vaccine group to determine the effect of antibody titer on the incidence of influenza. Then, the relationship between the occurrence of influenza and antibody titer level will be modeled using the logistic regression model advocated by Dunning that accommodates both antibody titers and factors independent of antibody titers.

In this model, the probability that a subject develops influenza is the probability that the subject is susceptible multiplied by the probability that susceptible individuals develop disease. Susceptibility is characterized by the probability l, and the probability that a subject with titer t is protected is represented by a 2-parameter logit function. Analyses will be conducted to determine the level of HI (or other assays that might be performed) antibody titer associated with 50%, 60%, 70%, 80% and 90% probability of protection.

The statistical and modelling considerations of estimating correlates of protection will further described in the SAP.

8.5 Sample Size and Power Considerations of Primary and Secondary Objectives

Efficacy objectives:

Sample size and power consideration for the aQIV efficacy objective is based on criteria for demonstrating efficacy in placebo controlled studies provided in CBER guidance, specifically that the study should be powered to assess the lower bound of the two-sided 95% CI of vaccine effectiveness, anticipated to be substantially above zero. This study is planned using a group sequential design. The power of Cox Regression which is planned to be used for analysis is dependent on the overall number of influenza cases, so the sample sizes on number of subjects described in this section is provided more for operational reasons. Additional information on the planning of number of subjects that may need to be enroled if it is decided to continue enrolment after interim analyses is described in Section 8.6.

For the primary efficacy objective: with 1-sided alpha of 2.5% and assuming an attack rate of influenza of 3.5% among subjects enroled in the non-influenza comparator group and 1.4% among the aQIV group, i.e. 60% assumed vaccine efficacy for aQIV, 238 events (i.e. 4,860 subjects per group under the assumed ERs) are needed with 86.5% power to show the absolute efficacy of aQIV versus non-influenza comparator, in preventing first occurrence RT-PCR-confirmed influenza A and/or B, due to any strain of influenza regardless of antigenic match to the strains in aQIV, in subjects ≥ 65 years of age, using a margin of 40% for lower bound of the CI for absolute vaccine efficacy.

For the first secondary efficacy objective: with a group vaccine efficacy of 65% but expecting conservatively reduced event rates of influenza cases due to matched strains of 2.5% among subjects in the non-influenza comparator group and 0.9% among the aQIV group then 144 events has estimated power approximately 88.5% to show the absolute efficacy of aQIV versus non-influenza comparator, using a margin of 40% for lower bound of the CI.

Assuming a drop-out rate of 10%, approximately 10,692 subjects ≥ 65 years, 5,346 per vaccine group will be randomized to receive either aQIV or non-influenza comparator (Boostrix®) in a 1:1 allocation ratio, stratifying by age (≥ 65 to 74 and ≥ 75 years of age), study site and by low vs high risk of influenza complications (score <50 vs ≥ 50).

Immunogenicity objective:

Anti-HA antibody will be measured using a validated haemagglutination inhibition (HI) assay with egg-derived HA antigens from homologous strains of the virus.

The immunogenicity objective is considered as secondary and so no alpha adjustment for multiplicity will be done for the analysis therefore a significance level of 5% (2-sided) or 2.5% (1-sided) was used for sample size calculation. One season in which at least 2800 subjects are anticipated to be enrolled will be selected for the collection of immunogenicity samples. Samples from approximately 2800 subjects participating in the immunogenicity season will be obtained. In order to maintain the study blind blood samples from an equal number of subjects participating in both treatment groups will be collected at Day 1 (baseline) and Day 22 (visit 3).

After all of the specimens have been obtained a subset of samples from those collected will be randomly selected on a 4:1 ratio for analysis. In total approximately 1,702 samples are planned to be included the analysis (1,362 aQIV; 340 Boostrix). The details and the guidelines regarding the selection process of these samples can be found in the SAP.

Following assumptions from the V70_27 study in elderly adult subjects were used: specifically after aTIV vaccination, seroconversion rates, H1N1: 77%, H3N2: 74% and B: 47%, and percentages of subjects with a HI titer ≥ 40, H1N1: 91%, H3N2: 99%, B: 64%.

With samples from at least 1,362 enroled subjects (1,226 evaluable subjects assuming a rate of 10% for missing data in the aQIV group) there will be enough power to evaluate achievement of CBER criteria with all four strains contained in the vaccine (see Table 8.5-1).

Table 8.5-1: Power to assess CBER criteria for subjects ≥ 65 years of age

Strain	π_i (proportion in aQIV, based on data of V70_27)	π_0 (CBER threshold)	Sample size for aQIV	Marginal Power
Proportion of subjects with Seroconversion				
H1N1	77%	30%	1226	99%
H3N2	74%	30%	1226	99%
B strains	47%	30%	1226	99%
Proportion of subjects with HI titer ≥ 1:40				
H1N1	91%	60%	1226	99%
H3N2	99%	60%	1226	99%
B strains	64%	60%	1226	82%

Safety objectives:

With 4,860 evaluable subjects in each treatment group, the probability of detecting a rare safety event which occurs at 0.001 (1/1000) rate will be 99%. With 1,000 evaluable subjects in each treatment group of the Solicited Safety Set, the probability of detecting an event which occurs at a rate of 0.002 will be ≥86%, assuming a drop-out/missing data rate of up to 5%.

Sample size calculations were performed using nQuery 7.0 and SAS 9.2.

8.6 Interim Analysis

As the circulation of influenza viruses is seasonal and the rates of influenza are difficult to predict, this study is group sequentially designed with maximally 2 interim analyses planned over the course of the study. The goal of Interim analyses is, first, to minimize the risk of not being able to take a significant test decision after the end of the study, and second, to be able to stop the study for early evidence of efficacy or for futility after observing at least 50% of planned ILI-cases.

- If the number of RT-PCR confirmed influenza cases is less or equal to 119 overall, no interim analysis for efficacy and futility will be done and the study will be continued because the probability to make a conclusion for futility or efficacy is too low.
- If the number of influenza cases ranges equal to 120 but less than 238 unblinded interim analyses for efficacy and futility will be performed by an independent Data

Monitoring Committee (DMC). To maintain the overall 95% significance level (α = 2.5%, 1-sided) for primary objective testing, an error-spending-function will be used.

The benefit of using an error-spending-function is that no maximum number of analysis stages and the timing of the analyses need to be pre-specified, what in practice means that the duration of the study in terms of number of seasons can be left open. Error-spending function is applied to calculate α-boundaries, forming the adjusted probabilities for the type 1 error. If the p-value for primary objectives test is lower than the respective α-boundary the trial stops early (i.e. without reaching the targeted number of cases of 238) for efficacy. Similarly β-boundaries are calculated, i.e. the adjusted probabilities for the type 2 error β, and if the p-value is higher than the β-boundary, the trial stops early for futility at that stage. In other words the trials stops early for futility, when the data provides sufficient evidence that the alternative hypotheses is not true, i.e. that the test vaccine is not as good as expected. Otherwise, the trial continues enrolment. Decisions to stop or continue the trial will be made on the basis of discussions between the DMC and Sponsor's Senior Management.

- If the number of influenza cases is greater or equal to 238 (targeted number of cases to be able to evaluate the primary objective) the trial will be stopped, data will be unblinded and the final analysis will be performed by the Sponsor. If the trial proceeds to the final analysis (upon reaching 238 cases) the boundaries for acceptance or rejection are identical to the assumed type 1 and type 2 errors for the overall design, and the trial stops to either reject or not reject the null hypothesis of the primary objective.

In case DMC states that the observed data provides already the full information level needed for the final test decision, then the final analysis can be done on full alpha level and no further enrolment is needed. However if the decision of the group-sequential test is to continue the study then it is on the DMC to determine the number of subjects needed to be additionally enroled. The monitoring committee should not be influenced by the results of the efficacy testing at the interim analysis when planning further subjects' accrual or the times of future analysis. Only the overall number of cases is allowed to be used for further planning. The following formula for determination of sample sizes for further enrolment may be used:

$$N_{total} = (C_{planned} - C_{observed}) * 200 / (ER_{aQIV} + ER_{Comp}),$$

where N_{total} denotes the total number of subjects needed for further enrolment, $C_{planned}$ is the overall number of cases needed for the test, i.e. 238 cases, $C_{observed}$ is the number of cases observed at current stage, and ER are the respective ERs assumed for each treatment group, i.e. 1.4 for aQIV and 3.5 for non-influenza comparator. A drop-out rate of 10% should be added.

For the analysis of early stopping for futility and for efficacy, an error-spending function will be applied to provide statistical stopping rules for efficacy (α-boundaries) and futility (β-boundaries) for the first interim analysis and second interim analysis, if necessary, based on the information accumulated until that specific interim stage, i.e. based on the accumulated variance of the parameter of interest.

These boundaries will be calculated on a p-value scale (https://support.sas.com/documentation/onlinedoc/stat/131/seqdesign.pdf)

At each interim stage, α-boundaries, forming the adjusted probabilities for the type 1 error, are calculated using error-spending function and if the p-value for the test of primary objective is lower than the respective α-boundary the trial stops for efficacy at this stage. Using the same error-spending-function applied on the overall type 2 error of 0.1 (Power 90%), β-boundaries are calculated, i.e. the adjusted probabilities for the type 2 error β, and if the p-value is higher than the β-boundaries, the trial stops early for futility at this stage.

In other words the trial stops early for efficacy if data collected at this stage allows to demonstrate primary efficacy objective (reject null-hypothesis); and the trial stops early for futility, if the data provides sufficient evidence that the test vaccine is not good as expected (the alternative hypotheses of absolute vaccine efficacy over the protocol-specified margin is not true, i.e VE<0.4). Otherwise, the trial continues to the next stage and more subjects will be enrolled.

The cumulative O'Brien-Fleming type error-spending-function (Lan and DeMets, 1983; option ERRFUNCOBF in SAS® PROC SEQDESIGN) will be used for both α- and β-boundaries; the error-spending function is defined as:

$$E(t;a) = \begin{cases} 1 & \text{if } t \geq 1 \\ \frac{1}{a}\,2\,(1-\Phi(\frac{z_{(1-a/2)}}{\sqrt{t}})) & \text{if } 0 < t < 1 \\ 0 & \text{otherwise} \end{cases}$$

where a equals α for α spending function and β for beta spending function, and where t is the information fraction.

With a specified type 1 error, α, and information level t at stage k, the cumulative error is αE(t; α) https://support.sas.com/documentation/onlinedoc/stat/131/seqdesign.pdf

If the trial proceeds to the final analysis, the boundary for rejection of null hypothesis is identical to the type 1 error (that is as the 0.025 one-sided alpha level)) with power specified for the overall design, and the trial stops to either reject or not reject the null hypothesis of the primary objective.

Additional interim analyses may be requested by the DMC, particularly if the first interim analysis is conducted soon after 119 cases of influenza have been reported. In this case, the DMC may request that a second interim analysis be conducted to allow for greater accuracy to determine if the trial should stop or continue.

Table 8.6-1 shows the needed total number of cases at each stage of the two-stage design together with boundaries for early stopping for futility or efficacy, calculated on p-value scale using the cumulative error spending function. With 1/2 information collected at the stage of interim analysis (that is, with exactly 119 confirmed ILIs) the trial would stop early for futility at this stage in case a p-value higher than 0.35022 is observed, or it would stop early for efficacy if the p-value is lower than 0.00625. Otherwise the trial will be continued and more subjects will be enrolled. The actual boundaries used for decision making would depend on number of confirmed ILIs occurring and reported for Interim Analysis.

Table 8.6-1: Example of a Two Stages Group-Sequential Design

	Stage 1 First Interim	**Stage 2 Final**
Number of Events	119	238
Alpha Boundary on p-value scale (equivalent to Type 1 error, 1-sided), early stopping for efficacy	0.00625	0.02275
Beta Boundary on p-value scale (equivalent to Type 2 error, 1-sided), early stopping for futility	0.35022	0.02275

The stopping rules given above are statistical and should be completed with clinical and strategic stopping rules that allow the DMC to make a decision on a broader picture of the data which includes safety endpoints and the other endpoints of the study. Another interim look at the data with appropriate adjustment of type 1 error might be recommended before reaching the targeted 238 cases.

Further details of the statistical methods are provided in the SAP and more information regarding clinical or strategic stopping rules will be provided in the DMC charter.

For the interim analyses, if needed a restricted unblinding will be done, i.e. only independent DMC members and unblinded individuals responsible for the analyses will receive access to the randomization codes and unblinded data for the purpose of preparing the interim analyses (further information on handling of the blinding for the interim analyses can be found in Section 3.3). The results of the interim analyses will be used only for DMC purposes and will not be reported in a Clinical Study Report (CSR).

9. SOURCE DOCUMENTATION, STUDY MONITORING AND AUDITING

In order to ensure consistency across sites, study monitoring and auditing will be standardized and performed in accordance with the Sponsor's or delegated contract research organization's (CRO) SOPs and applicable regulatory requirements (e.g., FDA, European Medicines Agency (EMA), and ICH guidelines).

Prior to enrolment of the first study subject, Seqirus or delegate will train investigators and/or their study staff on the study protocol, all applicable study procedures, documentation practices and all electronic systems. CRFs supplied by the Sponsor must be completed for each enroled subject (see Section 8.3.1, All Enroled Set for definition of enroled subject). Documentation of screened but not enroled subjects must be maintained at the site and made available for review by the site monitor. Data and documents will be checked by the Sponsor and/or monitor.

9.1 Source Documentation

Prior to the start of the study, the site staff participating in the study conduct will be instructed on what documents will be required for review as source documents. The kinds of documents that will serve as source documents will be agreed between Sponsor or delegate and investigator and designees and specified in the SDA prior to subject enrolment.

In addition, source documentation **must** include all of the following: subject identification (on each page), eligibility and participation, proper informed consent procedures, dates of visits, adherence to protocol procedures, adequate reporting and follow-up of adverse events, documentation of prior/concomitant medication/vaccines, study vaccine receipt/dispensing/return records, study vaccine administration information, any data collected by a telephone conversation with the subject and date of completion and reason.

The subject must also allow access to the subject's medical records. Each subject must be informed of this prior to the start of the study and consent for access to medical records may be required in accordance with local regulations.

All safety data reported by subjects must be written down in source documents prior to entry of the data into eCRFs. If there are multiple sources of information (e.g., Subject Diary, verbal report of the subject, telephone contact details, medical chart) supporting the diagnosis of an adverse event, these sources must be identified in the source documents, discrepancies between sources clarified, the ultimate diagnosis must be justified and written in the source documents, and this diagnosis must be captured in the Adverse Event eCRF (AE eCRF). The AE eCRF must also capture which source(s) of

information were used to determine the adverse event (e.g., subject recall, medical chart, Subject Diary).

9.2 Study Monitoring, Auditing and Source Data Verification

Prior to enrolment of the first study subject, Seqirus or its designee (e.g., a CRO) will develop a Clinical Monitoring Plan to specify how centralized and/or on-site monitoring, including clinical specimens reconciliation, will be performed for the study. Study progress will be monitored by Seqirus or its designee as frequently as necessary to ensure:

- that the rights and well-being of human subjects are protected,
- the reported study data are accurate, complete, and verifiable from the source documents and
- the conduct of the study is in compliance with the current approved protocol/amendment(s), GCP and applicable regulatory requirements.

Contact details for the Seqirus team or its designee involved in study monitoring will be provided to the investigator. Study data recorded on eCRFs will be verified by checking the eCRF entries against source documents in order to ensure data completeness and accuracy as required by study protocol.

Data verification may also be performed through a centralized review of data (e.g., checking for outliers or other anomalies). Additional documents such as the investigator site file, pharmacy records, and informed consent documentation must also be available for review if requested. Arrangements for monitoring visits will be made in advance in accordance with the monitoring plan, except in case of emergency.

The investigator and/or site staff must make source documents of subjects enroled in this study available for inspection by Seqirus or its representative at the time of each monitoring visit and Sponsor audits, when applicable. These documents must also be available for inspection, verification and copying, as required by regulations, by officials of the regulatory health authorities (e.g., FDA, EMA and others) and/or ECs/IRBs. The investigator and study site staff must comply with applicable privacy, data protection and medical confidentiality laws for use and disclosure of information related to the study and enroled subjects.

10. DATA MANAGEMENT

10.1 Data Entry and Management

In this study, all clinical data (including, but not limited to, AE/SAEs, concomitant medications, medical history, and physical assessments), safety data, and immunogenicity data will be entered onto CRFs in a timely fashion by the investigator and/or the investigator's dedicated site staff. Data entered onto CRFs are stored on a secure website. The data collected on this secure website are assimilated into an electronic data capture (EDC) system, which is compliant with Title 21 Part 11 policies of the Code of Federal Regulations (FDA 1997). The data system includes password protection and internal quality checks. The EDC system will be designed and validated by the Sponsor prior to activation for data entry by sites. The investigator or designated delegate must review data entered and electronically sign the CRFs to verify their accuracy.

Access to the EDC system for data entry or review will require training and distinct individual access code assignments to those site staff members who will be entering study data and those involved in study oversight who may review study data. Data are collected within the EDC system, to which the Sponsor and site monitors have exclusively "read only" access.

10.2 Data Clarification

As part of the conduct of the trial, the Sponsor may have questions about the data entered by the site, referred to as queries. The monitors and the Sponsor are the only parties that can generate a query. All corrections and clarifications will be entered into the EDC system and will be identified by the person entering the information, the reason for the change, as well as the time of the changes made. If changes are made to a previously and electronically signed CRF, the investigator must confirm and endorse the changes.

10.3 Data Protection

Seqirus respects the subjects' rights to privacy and will ensure the confidentiality of their medical information in accordance with all applicable laws and regulations.

The Sponsor as Data Controller according to the European Directive on the protection of individuals with regard to the processing of personal data and on the free movement of such data (95/46/EC) confirms herewith compliance to Directive 95/46/EC in all stages of Data Management.

11. RECORD RETENTION

Investigators must retain all study records required by Seqirus and by the applicable regulations in a secure and safe facility. The investigator must consult a Seqirus representative before disposal of any study records, and must notify the Sponsor of any change in the location, disposition, or custody of the study files. Essential documents must be retained for 15 years. “Essential documents” are defined as documents that individually and collectively permit evaluation of the conduct of a study and the quality of the data produced. These documents should be retained for a longer period, however, if required by the applicable national regulatory or institutional requirements.

Laboratory samples, provided that the integrity of the stored sample permits testing, will be retained up to 15 years.

12. USE OF INFORMATION AND PUBLICATION

Seqirus assures that the key design elements of this protocol will be posted in a publicly accessible database such as clinicaltrials.gov, and in compliance with current regulations.

Seqirus also assures that key results of this clinical study will be posted in a publicly accessible database within the required time-frame from the end of study as defined in Section 3.9, End of Study.

In accordance with standard editorial, ethical practices and current guidelines of Good Publication Practice (Graf 2009), Seqirus will generally support publication of multicenter studies only in their entirety and not as individual center data. In this case, a coordinating investigator will be designated by mutual agreement prior to the start of the study. The coordinating investigator will also sign the clinical study report on behalf of the principal investigators. Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements. Any formal publication of the study in which contribution of Seqirus personnel exceeded that of conventional monitoring will be considered as a joint publication by the investigator and the appropriate Seqirus personnel.

Seqirus must be notified of any intent to publish data collected from the study and prior approval from Seqirus must be obtained prior to submission for publication.

13. ETHICAL CONSIDERATIONS

13.1 Regulatory and Ethical Compliance

The study will be conducted in compliance with the protocol, GCP and applicable regulatory requirement(s).

This clinical study was designed and shall be implemented and reported in accordance with the ICH Harmonized Tripartite Guidelines for Good Clinical Practice, with applicable local regulations: including European Directive 2001/20/EC, US Code of Federal Regulations Title 21, and Japanese Ministry of Health, Labor, and Welfare, Seqirus codes on protection of human rights, and with the ethical principles laid down in the Declaration of Helsinki (European Council 2001, US Code of Federal Regulations, ICH 1997).

13.2 Informed Consent Procedures

Eligible subjects may only be included in the study after providing written informed consent or assent, as described in Section 5.1.1, Informed Consent/Assent. Before the start of the study, the investigator will have the informed consent and any other materials that will be provided to the subjects reviewed and approved by the IRB/EC. This review and approval will be documented and stored with other study documents. The investigator or designee must fully inform the subject or legal guardian of all pertinent aspects of the study. A copy of the written informed consent will be given to the subject or the designee. The subject/designee must be allowed ample time to ask about the details of the study and to make a decision as to whether or not to participate in the study. The subject and/or legal guardian(s) **must** sign the consent form indicating their agreement to participate in the study before any study-related procedures are conducted. The informed consent process may be conducted up to 10 days prior to vaccination on Day 1. If the subject and/or legal guardian(s) is unable to read and write, a witness must be present during the informed consent discussion and at the time of informed consent signature.

Prior to the start of the study, Seqirus or delegate will provide to investigators a proposed ICF that complies with the ICH GCP guideline and regulatory requirements and is considered appropriate for this study. Any changes to the proposed consent form suggested by the investigator must be agreed to by Seqirus before submission to the IRB/EC and a copy of the approved version must be provided to the Seqirus monitor or delegate after IRB/EC approval.

13.3 Responsibilities of the Investigator and IRB/EC

The protocol and the proposed ICF must be reviewed and approved by a properly constituted IRB/EC before study start. Properly constituted IRB/EC is defined in ICH Guideline for Good Clinical Practice E6 (R1), Section 3 (ICH 1997). A signed and dated statement that the protocol and informed consent have been approved by the IRB/EC must be given to Seqirus or delegate before study initiation. Prior to study start and at any time the protocol is amended during study conduct, the investigator is required to sign a protocol signature page confirming his/her agreement to conduct the study in accordance with these documents and all of the instructions and procedures found in this protocol and to give access to all relevant data and records to Seqirus monitors, auditors, Seqirus Clinical Quality Assurance representatives, designated agents of Seqirus, IRBs/ECs, and regulatory authorities as required. If an inspection of the clinical site is requested by a regulatory authority, the investigator must inform Seqirus immediately that this request has been made.

The investigator also responsible for the following:

- Maintaining a list of appropriately qualified persons to whom the investigator has delegated significant study-related duties.
- Demonstrating the capability of recruiting the required number of suitable subjects within the recruitment period.
- Demonstrating sufficient time and staffing to properly conduct and complete the study within the agreed study period.
- Ensuring that all persons assisting with the study are adequately informed about the protocol, the investigational product(s), and their study-related duties and functions
- Ensuring that appropriately trained health care professionals are responsible for all study-related medical decisions and for ensuring appropriate medical care of subjects experiencing any adverse event related to the study.
- If permission to do so is given by the subject or legal guardian, ensuring that the subject's primary healthcare provider is informed of the subject's participation in the study.

The investigator should not implement any deviation from, or changes of the protocol without agreement by the Sponsor and prior review and documented approval/favourable opinion from the IRB/IEC of an amendment, except where necessary to eliminate an immediate hazard(s) to study subjects, or when the change(s) involves only logistical or administrative aspects of the study (e.g., change in monitor(s), change of telephone number(s)). In addition, the investigator, or person designated by the investigator, should document and explain any deviation from the approved protocol.

The investigator may implement a deviation from, or a change of, the protocol to eliminate an immediate hazard(s) to study subjects without prior IRB/IEC approval/favourable opinion. As soon as possible, the implemented deviation or change, the reasons for it, and, if appropriate, the proposed protocol amendment(s) should be submitted:

(a) to the IRB/IEC for review and approval/favourable opinion,

(b) to the Sponsor for agreement and, if required,

(c) to the regulatory authority(ies).

13.4 Protocol Amendments

An amendment is a written description of change(s) to or formal clarification of a study protocol which may impact on the conduct of the clinical study, potential benefit of the clinical study, or may affect subject safety, including changes of study objectives, study design, subject population, sample sizes, study procedures, or significant administrative aspects. An administrative change of a study protocol is a minor correction or clarification that has no significant impact on the way the clinical study is to be conducted and no effect on subject safety (e.g., change of telephone number(s), logistical changes). Protocol amendments must be approved by Seqirus, health authorities where required, and the IRB/EC. In cases when the amendment is required in order to protect the subject safety, the amendment can be implemented prior to IRB/EC approval. Notwithstanding, the need for formal approval of a protocol amendment, the investigator is expected to take any immediate action required for the safety of any subject included in this study, even if this action represents a deviation from the protocol. In such cases, Seqirus should be notified of this action, the IRB/EC at the study site, and, if required by local regulations, the relevant health authority) should be informed within 10 working days.

14. REFERENCE LIST

59th World Medical Association General Assembly (October 2008). Declaration of Helsinki - Ethical Principles for Medical Research Involving Human Subjects. Seoul, Korea.

Ambrose, C. S. and Levin, M. J. (2012). "The rationale for quadrivalent influenza vaccines." Hum Vaccin Immunother 8(1): 81-88.

Beyer, W. E., J., McElhaney, et al. (2013). "Cochrane re-arranged: support for policies to vaccinate elderly people against influenza." Vaccine 31(50): 6030-6033.

Clopper CJ, Pearson ES. The use of confidential or fiducial limits illustrated in the case of the binomial. Biometrika 1934; 26:404-413

Code of Federal Regulations (1997): Food and Drug Administration, U.S. Department of Health and Human Services: Title 21, Part 11: Electronic Records Electronic Signatures. Federal Register 62: 13464.

De Villiers, P.J., Steele, A.D., et al. (2009) "Efficacy and safety of a live attenuated influenza vaccine in adults 60 years of age and older." Vaccine 28(1):228-34.

Dempster, A. L. (1977). Maximum likelihood from incomplete data via the EM algorithm. J R Stat Soc Series B Stat Methodol, 1-38.

DiazGranados, et al. (2014) "Efficacy of High-Dose versus Standard-Dose Influenza Vaccine in Older Adults" N Engl J Med. 317(7):635-645-91.

European Parliament (1995): Directive 95/46/EC of the European Parliament and of the Council of 4 April 2001. Official Journal of the European Communities. L 281/31-39.

European Parliament (2001): Directive 2001/20/EC of the European Parliament and of the Council of 4 April 2001. Official Journal of the European Communities. L 121/34-44.

Frey, S., et al. (2009). "Clinical Efficacy of Cell Culture–Derived and Egg-Derived Inactivated Subunit Influenza Vaccines in Healthy Adults". Clinical Infectious Diseases; 51(9):997–1004.

Frey, A. K. (2014). "Comparison of the Safety and Immunogenicity of an MF59®-adjuvanted with a Non-adjuvanted Seasonal Influenza Vaccine in Elderly Subjects." Vaccines. Manuscript Reference No.: JVAC-D-14-00218R1.

Goodwin, K., C. Viboud, et al. (2006). "Antibody response to influenza vaccination in the elderly: a quantitative review." Vaccine 24(8): 1159-1169.

Graf C, Battisti WP, Bridges D (2009). Good publication practice for communicating company Sponsored medical research: the GPP2 guidelines. BMJ; 339: b4330.

Gurfinkel, E., R. L. Fuente, et al. (2002). "Influenza Vaccine Pilot Study in Acute Coronary Syndromes and Planned Percutaneous Coronary Interventions: The FLU Vaccination Acute Coronary Syndromes (FLUVACS) Study." Circulation, 2143-2147.

Hak, E. F. (2004). Development and Validation of a Clinical Prediction Rule for Hospitalization Due to Pneumonia or Influenza or Death during Influenza Epidemics among Community-Dwelling Elderly Persons. Journal of Infectious Diseases, 450-458.

Heinze, G. and Schemper M. (2001). "A Solution to the Problem of Monotone Likelihood in Cox Regression." Biometrics, 57(1): 114-119.

ICH (1997). ICH Harmonised Tripartite ICH Guideline for Good Clinical Practices E6 (R1). Federal Register, 62 (90): 25691-25709.

ICH (1998). ICH Harmonised Tripartite ICH Guideline for Statistical Principles for Clinical Trials E9. Federal Register, 63 (179): 49583.

Jain VK, Rivera L, et al. (2013). "Vaccine for prevention of mild and moderate-to-severe influenza in children." N Engl J Med. 369(26):2481-91.

Jennison, C. T. (2000). Group sequential methods with applications to clinical trials. New York: Chapman and Hall.

Lo, Y. C., J. H. Chuang, et al. (2013). "Surveillance and vaccine effectiveness of an influenza epidemic predominated by vaccine-mismatched influenza B/Yamagata-lineage viruses in Taiwan, 2011-12 season." PLoS One 8(3): e58222.

Mannino, S., M. Villa, et al. (2012). "Effectiveness of Adjuvanted Influenza Vaccination in Elderly Subjects in Northern Italy." American Journal of Epidemiology, 176(6): 527-533.

MMWR Morb Mortal Wkly Rep (2010), 59(33): 1057-1062.

MMWR Morb Mortal Wkly Rep (2013), 62(49): 997-1000.

Mullooly, J. P., C. B. Bridges, et al. (2007). "Influenza- and RSV-associated hospitalizations among adults." Vaccine 25(5): 846-855.

Neuzil, K. M., B. G. Mellen, et al. (2000). "The effect of influenza on hospitalizations, outpatient visits, and courses of antibiotics in children." N Engl J Med 342(4): 225-231.

Nichol, K.L., J.D. Nordin, et al. (2007). “Effectiveness of Influenza Vaccine in the Community-Dwelling Elderly.” N Engl J Med 357(14): 1373-1381.

Osterholm, M. T., N. S. Kelley, et al. (2012). "Efficacy and effectiveness of influenza vaccines: a systematic review and meta-analysis." Lancet Infect Dis 12(1): 36-44.

Rubin, D. (1987). Multiple Imputation for Nonresponse in Surveys. New York: John Wiley and Sons.

Sasaki, S., M. Sullivan, et al. (2011). "Limited efficacy of inactivated influenza vaccine in elderly individual is associated with decreased production of vaccine-specific antibodies." J Clin Invest 121(8): 3109-3119.

Scheifele, D.W, S.A. Mcneil, et al. (2013). “Safety, immunogenicity, and tolerability of three influenza vaccines in older adults.” Results of a randomized, controlled comparison. Human Vaccines & Immunotherapeutics, 9(11): 1-14.

Treanor, J., et al (2011). "Protective efficacy of a trivalent recombinant hemagglutinin protein vaccine (FluBlok®) against influenza in healthy adults: A randomized, placebo-controlled trial". Vaccine 29: 7733– 7739.

U.S. Department of Health and Human Services, Food and Drug Administration, CBER (2009): Guidance for Industry Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims.

Van Buynder, P. G., S. Konrad, (2013). "The comparative effectiveness of adjuvanted and unadjuvanted trivalent inactivated influenza vaccine (TIV) in the elderly.” Vaccine 31: 6122-6128.

Villa, M., S. Black, et al. (2013). “Safety of MF59-Adjuvanted Influenza Vaccination in the Elderly: Results of a Comparative Study of MF59-Adjuvanted Vaccine Versus Nonadjuvanted Influenza Vaccine in Northern Italy.” American Journal of Epidemiology, 1-7.

http://www.cdc.gov/flu/about/disease/high_risk.htm Accessed 25 March 2015.

APPENDIX 1: EXAMPLES OF PRE-EXISTING MEDICAL CONDITIONS

1. Pulmonary Disease

a. Asthma
b. Chronic bronchitis
c. Chronic obstructive lung disease or emphysema
d. Pneumoconioses
e. Pulmonary fibrosis
f. Pulmonary tuberculosis and diseases due to other mycobacteria
g. Sarcoidosis

2. Heart Disease

h. Coronary artery disease
i. Valvular heart disease
j. Congenital heart disease
k. Hypertensive heart disease
l. Ischemic heart disease
m. Diseases of pulmonary circulation
n. Myocarditis
o. Arrhythmias, including atrial fibrillation
p. Congestive heart failure

3. Renal Disease

q. Hypertensive renal disease
r. Dialysis
s. Renal transplantation
t. Nephritis, nephrotic syndrome, nephrosis
u. Chronic pyelonephritis
v. Dialysis and transplant

4. Dementia or stroke

w. Neurologic and neurodevelopmental conditions [including disorders of the brain, spinal cord, peripheral nerve, and muscle such as cerebral palsy, epilepsy (seizure disorders), stroke, intellectual disability (mental retardation), moderate to severe developmental delay, muscular dystrophy, or spinal cord injury].

x. Cerebrovascular disease

y. Dementia

z. Hereditary and degenerative diseases of CNS

5. Non-hematological and hematological cancer (excluding cancer of the skin other than melanoma)

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