CLINICAL STUDY PROTOCOL V118_20 Version 1.0

A Phase 3, Randomized, Double-Blind, Controlled, Multicenter, Clinical Study to Evaluate Safety and Immunogenicity of an MF59-Adjuvanted Quadrivalent Subunit Influenza Vaccine in Comparison with an MF59-Adjuvanted Trivalent Subunit Influenza Vaccine and an MF59-Adjuvanted Trivalent Subunit Influenza Vaccine Containing the Alternate B Strain, in Adults Aged 65 Years and Above

Phase 3 Safety and Immunogenicity Study of aQIV in Elderly Adults

[redacted]

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PROTOCOL SYNOPSIS V118_20 VERSION 1

Name of Sponsor:	**Protocol number:**	**Generic name of study vaccine(s):**
Seqirus Inc.	V118_20	MF59-adjuvanted Quadrivalent Subunit Inactivated Egg-derived Influenza Vaccine (aQIV); Licensed MF59-adjuvanted Trivalent Subunit Inactivated Egg-derived Influenza Vaccine (aTIV-1); MF59-adjuvanted Trivalent Subunit Inactivated Egg-derived Influenza Vaccine Containing the Alternate B Strain (aTIV-2).

Title of Study: A Phase 3, Randomized, Double-Blind, Controlled, Multicenter, Clinical Study to Evaluate Safety and Immunogenicity of an MF59-Adjuvanted Quadrivalent Subunit Influenza Vaccine in Comparison with an MF59-Adjuvanted Trivalent Subunit Influenza Vaccine and an MF59-Adjuvanted Trivalent Subunit Influenza Vaccine Containing the Alternate B strain, in Adults Aged 65 Years and Above

Study Period: The total study period for a subject will be approximately 6 months following a single vaccination.	**Clinical Phase:** 3

Background and Rationale: Influenza is an infectious disease caused by the influenza virus, an orthomyxovirus with two clinically relevant types (types A and B). The disease is characterized by the abrupt onset of respiratory and systemic symptoms, such as fever, myalgia, headache, severe malaise, nonproductive cough, sore throat, and rhinitis, and occurs in epidemics throughout the northern and southern hemisphere winter months in temperate climates. During influenza epidemics, there is increased mortality among older adults (age $\geq$ 65 years) and people with chronic diseases, as well as an increase in morbidity and hospitalization because of influenza-associated complications.

The ability of vaccination to prevent influenza in older adults appears to be lower compared with younger adults, possibly because of a less robust immune response after influenza vaccination. One way to increase immunogenicity of influenza vaccines is through the use of adjuvants, such as the squalene and water emulsion adjuvant, MF59. Fluad, Seqirus' trivalent seasonal influenza vaccine adjuvanted with MF59, has been licensed for use in Europe since 1997 and in the US since 2015. It has been shown to generate significantly higher geometric mean hemagglutination inhibition (HI) titers and rates of seroconversion than a non-adjuvanted trivalent influenza vaccine comparator in

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elderly subjects. Trivalent influenza vaccines contain just one B strain antigen.

Influenza type B viruses, however, have separated into two distinct genetic lineages since 1985, Yamagata and Victoria. B strains from either lineage may circulate and cause infection, and mismatch may occur between circulating B strains and the strain contained in a trivalent vaccine. On average, influenza B strain accounts for approximately 25% of positive specimens in the US. Mismatches between the B strain in a trivalent vaccine and the circulating strain occur in approximately half of influenza seasons. To overcome this, several quadrivalent inactivated influenza vaccines are now licensed in the US, containing representative vaccine strains for both B-strain lineages, as well as the H1N1 and H3N2 A subtypes.

The investigational product (aQIV) is an MF59-adjuvanted subunit inactivated quadrivalent influenza virus vaccine. A 0.5 mL dose is formulated to contain 15 mcg hemagglutinin (HA) of each included influenza virus strain, including representative strains of both B lineages. The aQIV formulation is consistent with the currently licensed Fluad trivalent influenza virus vaccine (aTIV), except that it contains an additional B influenza strain so that the total HA concentration is 60 mcg HA/0.5 mL dose, from four strains.

The aim of this study is to demonstrate that inclusion of an additional B vaccine strain elicits an immune response to the second B virus and does not adversely impact the patient's immunogenicity response against strains previously included in trivalent formulations. Additionally, the aim is to demonstrate and confirm an acceptable safety and tolerability profile for the quadrivalent influenza vaccine formulation in the elderly population.

Data from this study will be used to support the licensure of aQIV for the prevention of seasonal influenza in adults $\geq$ 65 years of age.

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Study Objectives:

Co-Primary Immunogenicity Objectives:

1. To demonstrate that vaccination with aQIV elicits an immune response that is not inferior to that of an aTIV containing the same virus strains as the US licensed adjuvanted influenza vaccine (Fluad, aTIV-1), and an aTIV containing the alternate B strain (aTIV-2) among adults ≥65 years of age.
2. To assess the immunogenicity of aQIV in adults ≥65 years of age, based on the CBER (Center for Biologics Evaluation and Research) recommendations.

Secondary Immunogenicity Objectives:

The secondary objectives of the study are to assess the following, among adults aged ≥ 65 years:

1. To characterize the immunogenicity of aQIV, the aTIV-1 containing the same virus strains as the US licensed adjuvanted trivalent influenza vaccine, and the aTIV-2 containing the alternate B strain, by hemagglutination inhibition (HI).
2. To demonstrate the immunological superiority of aQIV compared to aTIV-1 and aTIV-2 for the B strain that is not included in each TIV vaccine separately;

Secondary Safety Objective:

1. To assess safety and tolerability of aQIV, aTIV-1, and aTIV-2 among adults ≥ 65 years of age.

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Exploratory Immunogenicity Objectives:

1. To explore the association between HI immune response after administration of aQIV or the aTIV-1, containing the same virus strains as the US-licensed adjuvanted trivalent influenza vaccine, and the aTIV-2 containing the alternate B strain by baseline characteristics.
2. Characterization of the immunogenicity of aQIV using other immunological assays (e.g., virus neutralization [MN] or anti-neuraminidase antibody assays may be performed).

Both exploratory objectives may be performed using either homologous or heterologous strains, or both.

Study Design: This phase 3 study is a randomized, double-blinded, comparator controlled, parallel-group, multicenter study of aQIV versus the US-licensed 2017-2018 adjuvanted trivalent influenza vaccine (aTIV-1, Fluad)**,** and versus an adjuvanted trivalent influenza vaccine (aTIV-2), containing the alternate B strain. All study vaccine administration will be a single dose, and consistent with the current license for aTIV-1.

The study will be conducted in approximately 1778 male and female adults aged 65 years and older who are healthy or have co-morbidities which increase their risk of complications from influenza infection. Subjects will be randomized to one of the three treatment groups in a 2:1:1 ratio. An Interactive Response Technology (IRT) system will be used for subject randomization.

Subjects will provide serological specimens during the two mandatory clinic visits before and after vaccination on Day 1 and Day 22 for measurement of immune responses in routine influenza assays. Each subject will complete a Diary Card for solicited local and systemic adverse events for 7 days after vaccination. Safety information will also be collected for all unsolicited AEs for 21 days following vaccination; and for the full duration of study participation for serious AEs (SAEs), AEs

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leading to withdrawal from the study, new onset of chronic diseases (NOCDs), AEs of special interest (AESIs), and concomitant medications associated with these events. Three scripted safety telephone calls will facilitate the collection of these safety data during the study period, and one reminder phone call will occur during the first few days after vaccination to remind the subject on the completion of the Diary Card.

An unscheduled study visit may be performed at any time during the study to further evaluate safety information described on the telephone.

Any subject who manifests signs of an influenza-like illness during the Treatment Period (Days 1-22) will be evaluated by real time reverse transcription polymerase chain reaction (RT-PCR) testing of a nasopharyngeal (NP) specimen for influenza. Subjects with onset of ILI and RT-PCR-confirmed influenza during the Treatment Period (Days 1-22) will be removed from the Per Protocol Set (PPS) in the immunogenicity analyses. ILI will also be recorded as an adverse event.

Number of Subjects planned: Approximately 1778 subjects will be enrolled into this study. In order to have 800 evaluable subjects in the aQIV group and 400 evaluable subjects in each aTIV group, and considering 10% for drop-outs, approximately 1778 are needed to be enrolled into this study. The subjects will be distributed among the vaccine groups in a ratio of 2:1:1 (aQIV:aTIV-1:aTIV-2).

Study Population and Subject Characteristics: This study will enroll males and females ≥65 years old who are healthy or have co-morbidities. The list of inclusion and exclusion criteria is included in protocol Section 4, Selection of Study Population.

Study Procedures:

Written informed consent must be obtained prior to any study-related procedures. The informed consent process may be conducted up to 10 days before day of vaccination (Day 1).

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Treatment Period: Day 1 through Day 22

After informed consent is signed by the subject or legal representative, on and prior to vaccination on Day 1, evaluations will be performed and will include relevant medical history, physical examination, and vital signs. A blood sample will be collected from all eligible subjects for influenza-specific serology testing. All eligibility assessments need to be completed prior to blood sample collection. Subjects will be assessed for risk of complications from influenza using the standardized scoring system described by Hak (2004).

All eligible subjects will then receive a single dose of 0.5 mL of study vaccine to which they were assigned, administered intramuscularly in the deltoid muscle, preferably of the non-dominant arm.

After vaccination, all subjects will remain under medical supervision at the study site for at least 30 minutes to be monitored and evaluated for local and systemic adverse events (AEs).

Subjects will receive a thermometer, a ruler, and a Diary Card, along with instructions to ensure proper completion; they will note any occurrence of solicited local and systemic AEs, and record their oral temperatures, preferably in the evening, for events occurring on Day 1 through Day 7. The Diary Card will only be used to collect solicited adverse events and temperature measurements.

A reminder telephone call will be made on Day 3 (window, Day 2 to Day 4) to remind the subject to complete the Diary Card and to return the Diary Card at the Day 22 clinic visit, when the Diary Card data and information on unsolicited AEs will be verbally collected and reviewed.

A scripted safety telephone call will be made by site staff to subjects on Day 15

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(window: Day 12 to day 18) to collect any unsolicited AEs and any use of concomitant medications: these will be captured in source documents and the electronic Case Report Form (CRF). Subjects with symptoms of ILI will be reminded to return to the study site for nasopharyngeal swab testing.

Subjects will return to the clinic on Day 22 (window, Day 19 to Day 25) for a medical examination, and to provide a serum sample for serologic testing. During this visit the Diary Card will be collected and all unsolicited AEs and concomitant medication use (occurring after vaccination between Day 1 and Day 22) will be documented in the subject's source records and captured in the CRF.

Any subject who manifests signs of an influenza-like illness (ILI, defined as 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) during the Treatment Period (Days 1-22) will be asked to come in to the site within 3 days of the onset of the ILI in order to have a nasopharyngeal (NP) swab collected for evaluation of the presence of influenza virus using RT-PCR. However, samples will be accepted if collected up to 6 days following the day of ILI onset. Swabs will be sent to a qualified central laboratory as specified in the Clinical Investigator Laboratory Manual.

Follow-up Period: Day 23 through Day 181

A scripted safety telephone call will be made on Day 91 (window: Day 84 to Day 98) to collect only those unsolicited AEs that are: serious AEs (SAEs), AEs leading to study withdrawal, new onset of chronic diseases (NOCDs), adverse events of special interest (AESIs); and concomitant medications associated with these events.

A scripted safety telephone call will be made on Day 181 (window: Day 167 to Day

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195) for assessment of SAEs, AEs leading to study withdrawal, NOCDs, and AESIs; and concomitant medications associated with these events.

An unscheduled study visit may be performed as necessary for further evaluation of safety information that is described on the telephone that is to be investigated further at any time during the study.

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

Study Vaccines: Regardless of the type of a vaccine assigned in the trial, subjects will receive a 0.5 mL dose. All three influenza vaccines are made similarly, with the exception of the influenza strains included.

Quadrivalent Influenza Test Vaccine (*aQIV, investigational vaccine*)

An adjuvanted inactivated subunit quadrivalent influenza vaccine, administered as one 0.5 mL intramuscular dose into the deltoid muscle. The vaccine is presented in a prefilled needleless syringe. Each 0.5 mL dose contains 15 mcg hemagglutinin (HA) from each of the following four influenza strains (recommended by the World Health Organization for the 2017-2018 Northern Hemisphere influenza season for quadrivalent vaccines:

- 15 mcg per 0.5 mL dose A/Michigan/45/2015 (H1N1)pdm09-like virus;
- 15 mcg per 0.5 mL dose A/Hong Kong/4801/2014 (H3N2)-like virus;
- 15 mcg per 0.5 mL dose B/Brisbane/60/2008-like virus (B/Victoria lineage):
- 15 mcg per 0.5 mL dose B/Phuket/3073/2013-like virus (B/Yamagata lineage).

Licensed Trivalent Influenza Comparator Vaccine 1 (aTIV-1, Trade name: Fluad)
An adjuvanted inactivated subunit trivalent influenza vaccine, administered as one 0.5 mL intramuscular dose into the deltoid muscle. The vaccine is presented in a prefilled

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needleless syringe.

Each 0.5 mL dose contains 15 mcg HA from each of the following three influenza strains (two influenza A strains and one B strain recommended for a trivalent influenza vaccine by the World Health Organization for the 2017-2018 Northern Hemisphere influenza season:

- 15 mcg per 0.5 mL dose A/Michigan/45/2015 (H1N1)pdm09-like virus;
- 15 mcg per 0.5 mL dose A/Hong Kong/4801/2014 (H3N2)-like virus;
- 15 mcg per 0.5 mL dose B/Brisbane/60/2008-like virus (B/Victoria lineage).

Trivalent Influenza Comparator Vaccine 2, with alternate B strain *(aTIV-2, investigational vaccine)*

An adjuvanted inactivated subunit trivalent influenza vaccine, administered as one 0.5 mL intramuscular dose into the deltoid muscle. The vaccine is presented in a prefilled needleless syringe. Each 0.5 mL dose contains 15 mcg HA from each of the following three influenza strains (two influenza A strains recommended for a trivalent influenza vaccine by the World Health Organization for the 2017-2018 Northern Hemisphere influenza season.and the alternate B strain to that recommended for TIV:

- 15 mcg per 0.5 mL dose A/Michigan/45/2015 (H1N1)pdm09-like virus;
- 15 mcg per 0.5 mL dose A/Hong Kong/4801/2014 (H3N2)-like virus;
- 15 mcg per 0.5 mL dose B/Phuket/3073/2013-like virus (B/Yamagata lineage).

Co-Primary Immunogenicity Endpoint(s):

The immunogenicity of study vaccines will be assessed 21 days (ie, on Day 22) after vaccine administration by measuring the hemagglutination inhibition (HI) antibody

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titers to the four virus strains included in the vaccines.

The noninferiority of aQIV compared to aTIV-1, and to aTIV-2 will be assessed for the eight co-primary endpoints of HI geometric mean titer (GMT) and seroconversion rate (SCR) for each virus strain included in the vaccines as follows:

- The GMT ratio* for the A/H1N1 strain;
- The GMT ratio for the A/H3N2 strain;
- The GMT ratio for the B strain (Yamagata lineage);
- The GMT ratio for the B strain (Victoria lineage);
- The difference between the SCR**for the A/H1N1 strain;
- The difference between the SCR for the A/H3N2 strain;
- The difference between the SCR for the B strain (Yamagata lineage);
- The difference between the SCR for the B strain (Victoria lineage).

Immunogenicity results obtained from aTIV-1 and aTIV-2 for both A/H1N1 and A/H3N2 strains will be pooled for comparison with aQIV.

**The GMT ratio is defined as the geometric mean of the post-vaccination (Day 22) HI titer for aTIV-1 (or aTIV-2) over the geometric mean of postvaccination (Day 22) HI titer for aQIV.*
***The SCR is defined as the percentage of subjects with either a prevaccination HI titer < 1:10 and a post-vaccination HI titer ≥ 1: 40 or a prevaccination HI titer ≥ 1:10 and a ≥ 4-fold increase in postvaccination HI titer.*

The second co-primary immunogenicity objective for aQIV will be assessed 21 days after vaccine administration by applying CBER criteria for the elderly population for each of the 4 strains included in aQIV:

- The percent of subjects achieving seroconversion for HI antibody

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- The percent of subjects achieving an HI antibody titer ≥ 1:40

The study is considered successful if the all co-primary endpoints are achieved.

Co-primary Immunogenicity Objective 1 - Criteria to demonstrate noninferiority:

In line with the FDA Guidance on seasonal inactivated influenza vaccines (Guidance for Industry Clinical Data Needed to Support Licensure of Seasonal Inactivated Influenza Vaccines 2007), aQIV will be considered to be noninferior to aTIV-1, containing the same virus strains as the US licensed adjuvanted trivalent influenza vaccine, and aTIV-2, containing the alternate B strain if, for each of the four strains, the following statistical criteria are met:

- The upper bound of the two-sided 95% confidence interval (CI) for the ratio of the GMTs (GMTr) does not exceed 1.5. The GMTr will be calculated as GMT_{aTIV}/GMT_{aQIV}; and
- The upper bound of the two-sided 95% CI for the difference between the SCRs does not exceed 10%. The difference in SCRs will be calculated as $SCR_{aTIV} - SCR_{aQIV}$

Co-primary Immunogenicity Objective 2 – CBER Criteria:

The endpoints for percent of subjects vaccinated with aQIV 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 (FDA, 2007):

- The lower bound of the two-sided 95% confidence interval for the percentage of subjects achieving seroconversion for HI antibody should meet or exceed 30%.
- The lower bound of the two-sided 95% confidence interval for the

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percentage of subjects achieving an HI antibody titer ≥ 1:40 should meet or exceed 60%.

The statistical evaluation consists of the observed proportion together with the corresponding two-sided 95% CI interval per strain.

No adjustment for type I error for multiplicity will be made. The study is successful if the co-primary immunogenicity objectives are achieved.

Secondary Immunogenicity Endpoint(s):

- The measures of immunogenicity of aQIV, aTIV-1 and aTIV-2 used for Secondary objective 1 as determined by the HI assay against homologous strains at Day 1 and 22 (unless indicated otherwise), include the following:
  - GMT: Geometric mean of HI titers on Day 1 and Day 22;
  - Geometric mean ratio (GMR)*: The geometric mean of the fold increase of postvaccination HI titer over the prevaccination HI titer (Day 22/Day 1);
  - The percentage of subjects with a titer ≥ 1:40 at Day 1 and Day 22;
  - SCR: the percentage of subjects with either a prevaccination HI titer < 1:10 and a postvaccination HI titer ≥ 1:40 or a prevaccination titer ≥ 1:10 and a ≥ 4-fold increase in postvaccination titer on Day 22.
- For secondary objective 2 the immunologic superiority HI antibody responses of the alternate B strain (the influenza B strain included in the aQIV but not in the aTIV formulation) in aQIV will be assessed separately, by the endpoints of the ratio of HI GMT and the difference of SCR for each B virus strain 21 days after the last vaccination in subjects. Superiority of aQIV over aTIV-1 and aTIV-2 for antibody response to the alternate B strain will be assessed using the GMT ratio (aTIV/aQIV) and difference in SCR (aTIV – aQIV) at Day 22. Point estimates and 95% confidence limits will be obtained as described for the primary endpoint. Superiority will be declared if the upper limit of the two-

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sided 95% CI for the difference in SCR (aTIV – aQIV) is < 0 and the upper limit of the two sided 95% CI for the GMT ratio (aTIV/aQIV) is < 1 for both B strains

Secondary Safety Endpoints:

Safety and tolerability will be assessed by the frequency and severity of:

- Solicited local and systemic adverse events (AEs) for 7 days following vaccination (Day 1 through Day 7)
- All unsolicited AEs for 21 days following vaccination (Day 1 through Day 22)
- Serious AEs (SAEs), AEs leading to withdrawal from the study, new onset of chronic diseases (NOCDs), AEs of special interest (AESIs), and concomitant medications associated with these events as collected from Day 1 through Day 181.

Exploratory Endpoint(s):

- Exploratory immunogenicity endpoints include:
  - GMTs: Geometric mean HI titers (GMTs) at Day 1 and Day 22
  - SCRs: Percentage of subjects with either a prevaccination HI titer < 1:10 and a postvaccination HI titer ≥ 1:40, or a prevaccination titer ≥ 1:10 and a ≥ 4-fold increase in postvaccination titer at Day 22
- In case of any additional optional immunogenicity analyses, such as MN, or assessments using heterologous influenza strains, the immune response will be characterized in a similar manner as described in the secondary

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immunogenicity endpoints section above.

Further details regarding the endpoints and analyses of these assays will be described in the Statistical Analysis Plan (SAP) prior to unblinding.

Statistical Analyses:

Sample Size Estimation:

aQIV will be tested against aTIV comparators. The treatment randomization ratio is 2:1:1 (aQIV: aTIV-1: aTIV-2). This study is powered to achieve 80% power to demonstrate noninferiority over 8 co-primary endpoints, seroconversion rates for 4 strains, GMT for 4 strains using a one-sided alpha of 0.025 for each comparison. No adjustment for multiple endpoints will be made.

For comparisons of SCR a noninferiority margin of 10% (aTIV – aQIV) will be employed. It is assumed that the SCRs for A/ H1N1, A/ H3N2 and B strains for TIV are 73%, 73% and 40% respectively. These estimates are based on the estimated SCR rates of historical data, namely study protocol V70_27. It has been assumed that there is no difference in terms of SCR between aQIV and aTIV for all strains. For comparison of GMT ratio a noninferiority margin of 1.5 (aTIV/aQIV) will be employed. It is assumed that there is no difference between aQIV and aTIV (i.e. a ratio of 1) and that the standard deviation of log (titer) is 1.2.

Under these assumptions, N evaluable = 800 in the aQIV group and 400 in each aTIV group providing 800 and 800 subjects receiving aQIV and aTIV respectively for comparisons of A strains, and 800 and 400 subjects receiving aQIV and aTIV respectively for comparisons of B strains. This provides a total N evaluable = 1600. These numbers provide 99.45% power to detect differences in SCR for each A strain and 91.29 % power for each B strain, providing overall 82.42% power for the 4 SCR

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tests.

For GMT ratio tests each A strain test will have 100% power and each B strain test will have 99.98% power, providing 99.96% power for the 4 GMT ratio tests and consequently 82.39% power for the 8 co-primary endpoints. Overall 1600 evaluable subjects will be required. Allowing for a 10% drop-out N=1778 subjects will be recruited (Sample size calculations were performed using PASS v12).

The immunogenicity was powered to meet the criteria prespecified in the CBER guidance for acceptable immunogenicity: namely,

- the lower bound of the two-sided 95% confidence interval for the percent of subjects achieving seroconversion should exceed 30%, and
- the lower bound of the two-sided 95% confidence interval for the percent of subject achieving HI antibody titer $\geq$ 40 should exceed 60%

With a sample size of N=800 (evaluable) subjects for the aQIV group if the population SCR for A/ H1N1, A/ H3N2 and B strains for TIV is 73%, 73% and 40% respectively then the probability of observing a seroconversion rate that is significantly greater than 30% is approximately 100% (for the A/H1N1), 100% for A/H3N2 and 100% (for the B-strains).

With a sample size of N=800 (evaluable) subjects for the aQIV group, if the population titer $\geq$ 1:40 rates for A/ H1N1, A/ H3N2 and B strains for TIV are 91%, 99% and 64.6% respectively (as observed in V70_27) then the probability of observing a SP rate that is significantly greater than 60% is approximately 100% (for the A/H1N1), 100% for A/H3N2 and 76.47% (for the B-strains).

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Analysis Populations:

The All Enrolled Set will comprise all subjects providing informed consent who are assigned a subject ID, and provide demographic and/or screening information.

The Full Analysis Set (FAS) will comprise all subjects randomized and receive a study vaccine.

The Safety Set will comprise all subjects in the FAS who received at least one dose of study vaccine and have provided follow-up safety data. This population will be used to summarize and list all safety information.

The Evaluable Population will comprise all subjects in the FAS who:

- receive vaccine on Day 1;
- provided pre- and postvaccination blood samples;
- did not experience laboratory-confirmed influenza illness; between Day 1 and Day 22; and
- did not receive any contraindicated medication during the study that is medically assessed to potentially impact immunogenicity results.

The Per Protocol Set will comprise all subjects in the evaluable population who do not have any protocol deviations felt to potentially impact immunogenicity results.

The Per Protocol Set will be the primary population of interest for the primary/secondary immunogenicity analysis and a supporting analysis will be performed using the Evaluable Population. Duplicate tables of primary and secondary immunogenicity analyses may also be produced based on the Evaluable population if there is >1% difference in the total number of subjects between the Per-Protocol

Name of Sponsor:	Protocol number:	Generic name of study vaccine(s):
Seqirus Inc.	V118_20	MF59-adjuvanted Quadrivalent Subunit Inactivated Egg-derived Influenza Vaccine (aQIV); Licensed MF59-adjuvanted Trivalent Subunit Inactivated Egg-derived Influenza Vaccine (aTIV-1); MF59-adjuvanted Trivalent Subunit Inactivated Egg-derived Influenza Vaccine Containing the Alternate B Strain (aTIV-2).

Population and the Evaluable Population.

Evaluation of Co-Primary Immunogenicity Endpoints:

Noninferiority

To determine the GMT ratio (adjusted analysis) a general linear model (GLM) will be fitted on log transformed (base 10) post-vaccination HI titer as the outcome variable and terms for covariates: vaccine treatment, pre-vaccination HI titer, age stratum (≥65-74, ≥75-84, and ≥85years), gender, vaccination history, age-by-vaccine interaction and study site. Potential covariate interaction effects will also be examined in the fit of the GLM. From the model, an adjusted difference in least square means (on the log scale) will be produced with 95% confidence limits. The estimated difference and the confidence limits will be back transformed to obtain an *adjusted GMT ratio* with 95% confidence limits. Each of the four strains will be analyzed separately. The adjusted GMT ratio will be the result for which the non-inferiority assessment of the HI GMT co-primary endpoint will be based on.

The statistical models might be reduced in case they fail to converge. Further details will be provided in the Statistical Analysis Plan

The complete set of covariates that will be used in the model to calculate the adjusted GMT ratio will include treatment group (3 treatments), age sub-group, sex (male or female), influenza vaccination received prior year (Y or N), prevaccination mean GMT titer (value) and investigator site (site identifier)

The GLM specification is: Adjusted Analysis GMT Model: Log-transformed Post-vaccination HI Titer = Vaccine + Age Strata + Gender + Vaccination History [y/n] + Log-transformed Prevaccination HI Titer + Site + Age Strata*Vaccine.

The measure of the *unadjusted* GMT ratio based on postvaccination GMTs only will

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also be presented.

In line with the FDA Guidance on seasonal inactivated influenza vaccines *(Guidance for Industry Clinical Data Needed to Support Licensure of Seasonal Inactivated Influenza Vaccines 2007)*. aQIV will be considered to be non-inferior to aTIV if, for each of the four strains, the following statistical criteria are met:

- The upper bound of the two-sided 95% Confidence Interval (CI) for the ratio of the GMTs does not exceed 1.5. The GMT ratio will be calculated by GMT_{aTIV}/GMT_{aQIV}.
- The upper bound of the two-sided 95% CI for the difference between the SCRs does not exceed 10%. The difference in SCR will be calculated by $SCR_{aTIV} - SCR_{aQIV}$.

CBER Criteria:

To achieve the co-primary CBER criteria:

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

To meet the CBER criteria, both endpoints should be met for each strain included in aQIV arm.

The statistical evaluation consists of the observed proportion together with the corresponding two-sided exact 95% confidence interval per strain. No adjustment for type I error for multiplicity is made.

Name of Sponsor:	**Protocol number:**	**Generic name of study vaccine(s):**
Seqirus Inc.	V118_20	MF59-adjuvanted Quadrivalent Subunit Inactivated Egg-derived Influenza Vaccine (aQIV); Licensed MF59-adjuvanted Trivalent Subunit Inactivated Egg-derived Influenza Vaccine (aTIV-1); MF59-adjuvanted Trivalent Subunit Inactivated Egg-derived Influenza Vaccine Containing the Alternate B Strain (aTIV-2).

Secondary Immunogenicity Endpoints:

Characterization of immunogenicity of aQIV, aTIV-1 and aTIV-2:

The measures of immunogenicity of aQIV, aTIV-1 and aTIV-2 will be assessed in terms of HI antibodies. Serum HI antibody titers against the 4 influenza vaccine strains will be used to calculate:

- GMT: Geometric mean of HI titers on Day 1 and Day 22;
- GMR: The geometric mean of the fold increase of post- vaccination HI titer over the pre-vaccination HI titer (Day 22/Day 1;
- The percentage of subjects with a titer ≥ 1:40 at Day 1 and Day 22;
- SCR: the percentage of subjects with either a prevaccination HI titer < 1:10 and a postvaccination HI titer ≥ 1:40 or a prevaccination titer ≥ 1:10 and a ≥ 4-fold increase in postvaccination titer on Day 22.

Superiority of immunologic response for aQIV vs aTIV:

Superiority of aQIV over aTIV-1 and aTIV-2 for antibody response to the alternate B strain will be assessed using the GMT ratio (aTIV/aQIV) and difference in SCR (aTIV – aQIV) at Day 22. Point estimates and 95% confidence limits will be obtained as described for the primary endpoint. Superiority will be declared if the upper limit of the two-sided 95% CI for the difference in SCR (aTIV – aQIV) is < 0 and the upper limit of the two sided 95% CI for the GMT ratio (aTIV/aQIV) is < 1 for both B strains.

Interim Analysis: An interim analysis is not planned for this study.

Data Monitoring Committee: An independent Data Monitoring Committee will not be utilized for the study.

Table 1: Time and Events Table

Assessment	Clinic Visit 1	Reminder Phone Call	Safety Phone Call	Clinic Visit 2	Safety Phone Call	Safety Phone Call[12]
	Day 1	Day 3 (-1 to + 1 days)	Day 15 (-3 to + 3 days)	Day 22 (-3 to + 3 days)	Day 91 (-7 to +7 days)	Day 181 (-14 to + 14 days)
EDC Visit no:	1	2	3	4	5	6
Informed consent[1]	✓					
Demographics and influenza vaccination history[2,3]	✓					
Medical history and baseline medication use[3]	✓					
Physical examination [3,4]	✓			✓		
Oral temperature, vital signs, height, weight[3]	✓					
Review of eligibility criteria[3]	✓					
Blood sample for immunogenicity testing[3]	✓			✓		
Vaccination[5,6]	✓					
Provision of study supplies and instructions[7,8]	✓					
Subject Diary Card reviewed and collected				✓		
Telephone contact[9]		✓	✓		✓	✓
Assess influenza-like illness (*if applicable*)[10]	✓	✓	✓	✓		
Assess all unsolicited adverse events and concomitant medications[11]			✓	✓		
Assess SAEs, NOCDs, withdrawal AEs, AESIs & associated medications	✓	✓	✓	✓	✓	✓

1. The invitation to participate and the informed consent process must be conducted within 10 days before the day of vaccination (Day 1)
2. Confirm that patient has had the opportunity to ask questions and consent form(s) are signed prior to any V118_20 procedures being performed.
3. Procedure to be performed prior to vaccination. All eligibility criteria must be met before any study procedures (eg., blood sampling) can be performed.
4. Physical examination must be performed by a qualified health care practitioner in accordance with local regulations and licensing requirements designated within the Site Responsibility Delegation Log.
5. Vaccination should occur only after the pre-dose blood sample collected.
6. After vaccination, the subject will remain under medical supervision for at least 30 minutes and observed for local and systemic AE and unsolicited AEs. A body temperature measurement (preferably oral) will be taken.
7. A Diary Card, thermometer and ruler will be dispensed at Day 1. Subject will receive instruction on diary completion and thermometer and ruler use.
8. On Day 1 approximately 6 hours after the vaccination or prior to going to bed at the latest, and daily thereafter through Day 7, solicited local and systemic adverse events including other adverse events (i.e., body temperature measurements and use of analgesics/antipyretics) will be reported daily by the subject in the Diary Card.
9. The reminder call at Day 3 will be made by site staff to remind the subject to complete the Diary Card. In the safety calls at Day 15, Day 91 and day 181, subjects will be interviewed by site staff using a scripted interview for collection of safety data. These safety data will be collected in source documents by the individuals performing the interviews.
10. The subject will be asked to contact the site staff if the subject experiences ILI symptoms[a] during the interval between Day 1 and Day 22 (i.e., up to and including the day of the Day 22 blood sample). The subject should visit the site within 3 days of the onset of the ILI in order for a nasopharyngeal swab sample to be taken, however samples will be accepted if collected up to 6 days following the day of ILI onset. The sample will be sent to the central laboratory for RT-PCR analysis.

[a] defined as 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: oral temperature of >37.2°C/ 99°F, chills, tiredness, headache, or myalgia.

11. All adverse events through the day 22 visit, and medications used to treat them.
12. Any subject who terminates the study prematurely after receiving a vaccination should have a termination visit/call (Section 5.5.1).

LIST OF ABBREVIATIONS

AE	Adverse Event
AESI	Adverse Event of Special Interest
CBER	Center for Biologics Evaluation and Research
CDC	Centers for Disease Control and Prevention
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
EDC	Electronic Data Capture
EMA	European Medicines Agency
FAS	Full Analysis Set
FDA	United States Food and Drug Administration
GCP	Good Clinical Practices
GMR	Geometric Mean Ratio
GMT	Geometric Mean Titer
GMTr	Geometric Mean Titer Ratio
HA	Hemagglutinin
HI	Hemagglutination Inhibition

HIPAA	Health Insurance Portability and Accountability Act
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Council (previously Conference) on Harmonisation of Technical Requirements for 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
PCR	Polymerase Chain Reaction
PP	Per Protocol
PPS	Per Protocol Set
PV	Pharmacovigilance
aQIV	Adjuvanted Quadrivalent Influenza Vaccine
QIV	Quadrivalent Influenza Vaccine
RT-PCR	Reverse Transcriptase Polymerase Chain Reaction
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan

SC	Seroconversion
SCR	Seroconversion Rate
SDA	Source Data Agreement
SOC	System Organ Class
SOP	Standard Operating Procedure
aTIV	Adjuvanted Trivalent Influenza Vaccine
TIV	Trivalent Influenza Vaccine
WHO	World Health Organization
VSAE	Vaccine Serious Adverse Event

1. BACKGROUND AND RATIONALE

1.1 Background

Influenza is an infectious disease caused by the influenza virus, an orthomyxovirus with two clinically relevant types (types A and B). The disease is characterized by the abrupt onset of respiratory and systemic symptoms, such as fever, myalgia, headache, severe malaise, nonproductive cough, sore throat, and rhinitis (Temte and Prunuske, 2010), and occurs in epidemics throughout the northern and southern hemisphere winter months in temperate climates. In general, influenza is resolved within two to seven days, although symptoms of cough and malaise may be prolonged. However, for some people, notably older adults and those with chronic diseases (such as pulmonary or circulatory disorders, metabolic disorders such as diabetes mellitus, renal dysfunction, or immunosuppression), influenza can exacerbate underlying medical conditions and/or lead to secondary viral or bacterial pneumonia (Rothberg et al., 2008; Fiore et al., 2009). During influenza epidemics, there is increased mortality among older adults (age > 65 years) and people with chronic diseases, as well as an increase in morbidity and hospitalization because of influenza-associated complications (Fiore et al. 2009; Monto 2008).

The ability of vaccination to prevent influenza in older adults appears to be lower compared with younger adults (Osterholm, Kelley et al., 2012; Beyer, McElhaney et al., 2013), possibly because of a less robust immune response after influenza vaccination (Goodwin, Viboud et al., 2006; Sasaki, Sullivan et al., 2011). One way to increase immunogenicity of influenza vaccines is through the use of adjuvants, such as the squalene and water emulsion adjuvant, MF59. Fluad, Seqirus' trivalent seasonal influenza vaccine adjuvanted with MF59, has been licensed for use in Europe since 1997 and in the US since 2015. It has been shown to generate significantly higher geometric mean hemagglutination inhibition (HI) titers and rates of seroconversion than a non-adjuvanted trivalent influenza vaccine comparator in elderly subjects (Frey et al., 2014).

Trivalent influenza vaccines contain just one B strain antigen. Influenza type B viruses, however, have separated into two distinct genetic lineages since 1985, Yamagata and Victoria (Rota et al., 1990). B strains from either lineage may circulate simultaneously (Ambrose and Levin, 2012) and cause infection, and mismatch may occur between circulating B strains and the strain contained in a trivalent vaccine (Lo, Chuang et al., 2013). On average, influenza B strain accounts for approximately 25% of positive specimens in the US. Mismatches between the B strain in a trivalent vaccine and the circulating strain occur in approximately 5 out of every 10 influenza seasons (Belshe, 2010). To overcome this, several quadrivalent inactivated influenza vaccines are now licensed in the US, containing representative vaccine strains for both B-strain lineages, as well as the H1N1 and H3N2 A subtypes.

1.2 Rationale

The investigational product (aQIV) is an MF59-adjuvanted egg-derived subunit inactivated quadrivalent influenza virus vaccine. A 0.5 mL dose is formulated to contain 15 mcg hemagglutinin (HA) of each influenza virus strain, including representative strains of both B lineages. The aQIV formulation is consistent with the currently licensed Fluad trivalent influenza virus vaccine (aTIV), but contains an additional B influenza strain so that the total HA concentration is 60 mcg HA/0.5 mL dose, from four strains.

The aim of this study is to demonstrate that inclusion of an additional B vaccine strain elicits an antibody response to that strain and does not adversely impact the immunogenicity response against strains previously included in trivalent formulations. Additionally, the aim is to demonstrate and confirm an acceptable safety and tolerability profile for the quadrivalent influenza vaccine formulation in the elderly population.

Data from this study will be used to support the licensure of aQIV for the prevention of seasonal influenza in adults ≥ 65 years of age.

2. OBJECTIVES

2.1 Primary Objectives

Co-Primary Immunogenicity Objectives:

1. To demonstrate that vaccination with aQIV elicits an immune response that is not inferior to that of an aTIV containing the same virus strains as the US licensed adjuvanted influenza vaccine (Fluad, aTIV-1), and an aTIV containing the alternate B strain (aTIV-2) among adults ≥65 years of age.
2. To assess the immunogenicity of aQIV in adults ≥65 years of age, based on the CBER (Center for Biologics Evaluation and Research) recommendations.

2.2 Secondary Immunogenicity Objectives

The secondary immunogenicity objectives of the study are to assess the following, among adults aged ≥ 65 years:

1. To characterize the immunogenicity of aQIV, the aTIV-1 containing the same virus strains as the US licensed adjuvanted trivalent influenza vaccine, and the aTIV-2 containing the alternate B strain, by hemagglutination inhibition (HI).
2. To demonstrate the immunological superiority of aQIV compared to aTIV-1 and aTIV-2 for the B strain that is not included in each TIV vaccine separately.

2.3 Secondary Safety Objective:

1. To assess safety and tolerability of aQIV, aTIV-1, and aTIV-2 among adults ≥65 years of age.

2.4 Exploratory Immunogenicity Objectives

1. To explore the association between HI immune response after administration of aQIV or the aTIV-1, containing the same virus strains as the US-licensed adjuvanted trivalent influenza vaccine, and the aTIV-2 containing the alternate B strain by baseline characteristics.
2. Additional optional objectives include characterization of the immunogenicity of aQIV using other immunological assays (e.g., virus neutralization [MN] or anti-neuraminidase antibody assays may be performed).

Both exploratory objectives may be performed using either homologous or heterologous strains, or both.

3. STUDY DESIGN

3.1 Overview of Study Design

This phase 3 study is a randomized, double-blinded, comparator controlled, parallel group, multicenter study of aQIV versus the US licensed 2017-2018 adjuvanted trivalent influenza vaccine (Fluad, aTIV-1), and versus an adjuvanted trivalent influenza vaccine, aTIV-2, containing the alternate B strain.

The study will be conducted during the 2017-2018 Northern Hemisphere influenza season in male and female adults aged 65 years and older who are healthy or have co-morbidities (Section 5.1.2) which increase their risk of complications from influenza infection. Subjects will be randomized to one of the three treatment groups in a 2:1:1 ratio. An Interactive Response Technology (IRT) system will be used for subject randomization.

Subjects will provide serological specimens before and after vaccination as well as complete Diary Cards for solicited local and systemic adverse events.

Each subject will have two stages of study participation: Treatment Period (Day 1 through Day 22) and Follow-up Period (Day 23 through Day 181).

Treatment Period: Day 1 through Day 22

Written informed consent must be obtained prior to any study-related procedures. The informed consent process may be conducted up to 10 days before the day of vaccination (Day 1). Prior to vaccination on Day 1, evaluations will be performed and will include medical history, physical examination, and vital signs. A blood sample will be collected from all eligible subjects for influenza-specific serology testing. All eligibility assessments need to be completed prior to blood sample collection. Subjects will be assessed for risk of complications from influenza using the scoring system described by Hak (2004).

All eligible subjects will then receive a dose of 0.5 mL of study vaccine to which they were assigned, administered intramuscularly in the deltoid muscle, preferably of the non-dominant arm.

After vaccination, all subjects will remain under medical supervision at the study site for at least 30 minutes to be monitored and evaluated for local and systemic adverse events (AEs).

Subjects will receive a thermometer, a ruler and a Diary Card, along with instructions to ensure proper completion, and will note any occurrence of solicited local and systemic AEs, and record their oral temperatures for events occurring on Day 1 through Day 7. The Diary Card will only be used to collect solicited adverse events.

A reminder telephone call will be made on Day 3 (window, Day 2 to Day 4) to remind the subject to complete the Diary Card.

A scripted safety telephone call will be made by qualified site staff on Day 15 (window: Day 12 to day 18) to collect any unsolicited AEs and any use of concomitant medications: these will be captured in the electronic Case Report Form (CRF).

Subjects will return to the clinic on Day 22 (window, Day 19 to Day 25) for a medical examination, and to provide a blood sample for serologic testing. During this visit Diary Cards will be collected and all unsolicited AEs and concomitant medication use (occurring after vaccination between Day 1 and Day 22) will be documented in the subject's source records and captured in the CRF.

Any subject who manifests signs of an influenza-like illness (ILI, defined as 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) during the may be performed at any time during the Treatment Period(Days 1-22) will be evaluated by real time reverse transcription polymerase chain reaction (RT-PCR) testing of a nasopharyngeal (NP) specimen for influenza. Swabs will be sent to a qualified central laboratory as specified in the Clinical Investigator Laboratory Manual. Subjects with onset of ILI and RT-PCR-confirmed influenza during the Treatment Period (Days 1-22) will be removed from the Per Protocol Set (PPS) in the immunogenicity analyses. ILI will also be recorded as an adverse event.

Follow-up Period: Day 23 through Day 181

A scripted safety telephone call will be made by qualified site staff on Day 91 (window: Day 84 to Day 98) to collect only those unsolicited AEs that are: serious AEs (SAEs), AEs leading to study withdrawal, new onset of chronic diseases (NOCDs), adverse events of special interest (AESIs); and concomitant medications associated with these events.

A scripted safety telephone call will be made by qualified site staff on Day 181 (window: Day 167 to Day 195) for assessment of SAEs, AEs leading to study withdrawal, NOCDs, and AESIs; and concomitant medications associated with these events.

An unscheduled study visit may be performed as necessary for further evaluation of safety information that is described on the telephone that is to be investigated further at any time during the study.

A clinical study report will present immunogenicity and safety data collected through the final evaluation (6 months following vaccination, Day 181).

3.2 Study Period

Each subject should expect to participate in the study for approximately 6 months from the time of enrollment through the last study visit (Day 181 phone call).

3.3 Blinding Procedures

The trial is designed as a double-blind study. There are no visible differences between the investigational aQIV vaccine and the two comparator aTIV vaccines. 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 administering the vaccines or clinical evaluation of the subject will be aware of the vaccine administered.

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 general, unblinding should only be performed when knowledge of the assigned treatment will affect a subject's management. 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 over the duration of their study participation:

- Medical History
- Vaccination History
- Demographic Information.
- All unsolicited AEs (from Day 1 through Day 22)
- Adverse Events (from Day 23 through Day 181):
  - AEs leading to withdrawal
  - AESIs

- NOCDs
- SAEs
- Concomitant Medications (as defined in Section 6.5)

- Reason for study termination

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

3.4.2 Tools Used for Data Collection

Data will be recorded in the Diary Card and collected on Case Report Forms (CRFs).

Diary Cards

Subjects will be given a paper diary at their Day 1 clinic visit to complete. The paper diaries, hereafter referred to as the Diary Card, will be the only source document allowed for solicited local and systemic adverse events (including body temperature measurements), starting after the initial 30 minute postvaccination period at the clinic through Day 7.

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

1. No corrections or additions to the information recorded by the subject or legal representative to the Diary Card will be allowed after it is delivered to the site.
2. Any blank or illegible fields on the Diary Card must be described as missing in the CRF.

Case Report Forms

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

Data should be entered into the CRF in a timely fashion following each subject's clinic visit, study procedure, or phone call. Each subject's CRF 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 Diary Card information collected in the CRFs:

1. The site must enter all readable entries in the Diary Card 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 representative. 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 Diary Card, 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 Diary Card 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:

- Blood at the Day 1 and Day 22 clinic visits
- Nasopharyngeal swabs (as needed from subjects experiencing symptoms that meet ILI criteria from Day 1 through Day 22)

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

Blood Specimens

Approximately 10 mL sample of blood will be drawn from all eligible subjects at Day 1 before vaccination and at Day 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 Day 1 to Day 22, experience symptoms meeting the ILI criteria (ie, 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.

3.6 Stopping/Pausing Guidelines

There are no predetermined stopping rules in this study. Subjects may be withdrawn from the study according to investigator discretion as described in Section 3.8, Premature Withdrawal from Study.

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. Further enrollment will only occur after written authorization is provided by the Sponsor in consultation with the health authorities and EC/IRB, as appropriate.

3.7 Data Monitoring Committee

An independent Data Monitoring Committee will not be utilized for the study.

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. 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 (see Section 7.1, Safety Assessments).

Death

For any subject withdrawn from study participation due to death, this should be noted on the Study Termination CRF page and the associated SAE that led to the death must be reported (see Section 7.1, Safety Assessments).

Withdrawal of consent

The subject (or their legally appointed representative) can withdraw consent for participation in the study at any time without penalty or loss of benefit to which the subject is otherwise entitled. If the subject withdraws consent for the study, no further study procedures will be performed with the subject.

If a subject withdraws consent but does not revoke the Health Insurance Portability and Accountability Act (HIPAA) authorization, the Sponsor will have full access to the subject's medical records, including termination visit information. If a subject 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 visits (clinic or telephone contacts), 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 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 CRF 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 prespecified withdrawal criterion, subject discontinuation for insurance issues, moving, no time, etc. This reason

should be noted in the Study Termination CRF page and any ongoing AEs at the time of study withdrawal must be followed until resolution/stabilization whenever possible.

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.

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.

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.

3.9 End of Study

Evaluation of the primary and secondary immunogenicity objectives requires the testing of biological samples from the study subjects, which can only be completed after all samples are collected. The last samples for the analysis of the primary and secondary immunogenicity objectives will be taken at Day 22. For the purpose of this protocol, end of study is defined as the completion of the Last Subject Last Visit (LSLV), i.e. the last subject's Day 181 safety phone call, or the completion of testing of biological samples, to be achieved no later than 8 months after LSLV, whichever is longer.

4. SELECTION OF STUDY POPULATION

4.1 Inclusion Criteria

Subjects must meet all of the following inclusion criteria to participate in this study:

1. Males and females ≥ 65 years old who are healthy or have co-morbidities
2. Individuals who or whose legal representative(s) 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 Diary Card completion and follow-up (and responding to messages and telephone contact). A subject or legal representative should be considered able to comply if the Investigator judges that the subject will complete the Diary Card when applicable, return for all the follow-up visits, and be available for telephone calls as scheduled in the study

4.2 Exclusion Criteria

If one or more of the following exclusion criteria are met, the subject will be ineligible to take part in this study:

1. 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
2. History of any medical condition considered an adverse event of special interest
3. Progressive or severe neurological disorder, seizure disorder, or history of Guillain-Barré syndrome
4. Hypersensitivity, including allergy, to any component of vaccines, medicinal products or medical equipment whose use is foreseen in this study
5. 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
6. Abnormal function of the immune system resulting from:
    a. Clinical conditions affecting the immune system (e.g. HIV infection, agammaglobulinemia)
    b. Systemic administration of corticosteroids (PO/IV/IM) at a dose equivalent to 20 mg/day of prednisone for more than 14 consecutive days within 90 days prior to informed consent
    c. Administration of antineoplastic and immunomodulating agents (eg, TNF α- antagonists or anti-B cell antibodies) or radiotherapy within 1 year prior to informed consent

7. Receipt of immunoglobulins or any blood products within 180 days prior to informed consent
8. Receipt of an investigational or nonregistered medicinal product within 30 days prior to informed consent or before completion of the safety follow-up period in another study, or 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)
9. Study personnel or immediate family members (brother, sister, child, parent), the spouse of personnel with direct involvement in the study
10. Receipt of any influenza vaccine within 6 months prior to enrollment in this study, or plan to receive influenza vaccine prior to the Day 22 blood collection
11. Receipt of any inactivated non-influenza vaccine 14 days or live-attenuated vaccine 28 days prior to enrollment in this study or plans to receive any other non-influenza vaccine within 28 days from study vaccination
12. Fever at the time of screening, defined as oral temperature ≥38.0 degrees Celsius (≥100.4° F). Enrollment could be considered if fever is absent for 72 hours
13. Signs or symptoms of acute infection at the time of screening. Enrollment could be deferred if signs and symptoms are absent for 72 hours
14. Fatal prognosis of an underlying medical condition (<12 months life expectancy)
15. 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: body temperature elevation [≥38.0°C (≥ 100.4° F) within 3 days prior to intended study vaccination], 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 enrollment after the appropriate window for delay has 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.

Table 5 Study Procedures

Visit Category	Procedures
Prevaccination Clinic Visit	Section 5.1 describes procedures to be followed prior to study vaccination: informed consent, screening, enrollment, and randomization
Vaccination Clinic Visit	Section 5.2 describes procedures to be followed during the vaccination clinic visit: vaccination, post-vaccination procedures, and post-vaccination reminder call
Postvaccination Visit/Call(s)	Section 5.3 describes follow-up clinic visits and safety follow-up calls
Unscheduled Visit(s)	Section 5.4 describes possible procedures to be followed at unscheduled clinic visit
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 Prevaccination Clinic Visit(s)

This section describes the procedures that must be performed for each potential subject prior to vaccination, including obtaining informed consent, screening, enrollment and randomization.

5.1.1 Informed Consent

"Informed consent" is the voluntary agreement of an individual or his/her legal representative(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 of the subject following local IRB/EC guidance **must** be obtained before conducting any study-specific procedures (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. Additional specifics regarding the informed consent and assent processes are located in Section 13.2, Informed Consent Procedures.

If a subject 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 the subject's legally acceptable representative cannot read, and who reads the informed consent form and any other written information supplied to the subject. After the written informed consent form and any other written information to be provided to subjects, is read and explained to the subject or legal representative and after the subject or legal representative has verbally consented to the subject's participation in the study and, if capable of doing so, has signed and personally dated the informed consent form, 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 representative and that informed consent was freely given by the subject or legal representative.

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 manually created by the Investigator. The subject's unique Screening Number will be documented in the Screening and Enrollment 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 enrollment, demographic data will be collected from the subject, including: age, sex, race, ethnicity, height and weight, prior influenza vaccination, 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.

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

medical conditions are presented in Appendix 1 as examples for the Investigator to facilitate the completion of the co-morbidity section of the risk score.

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[b]	
0	0
1-6	11
7-12	22
>13	33
Previous hospitalization due to pneumonia or influenza	
No	0
Yes	63
Comorbidity[c]	
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] Scheduled and unscheduled face-to-face visits with a physician or other health-care providers, including annual examinations, or visits to urgent care and emergency departments [c] 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.

Only the total risk score will be recorded in the CRF; pre-existing medical conditions should be recorded in the source documentation. The risk score will be collected for each subject, but will not be used to stratify treatment.

Medical history will 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 can 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 representative as to any complaints the subject has experienced across each organ system. This will be performed before enrollment 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 prevaccination 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, must 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, approximately 10 mL of blood will be drawn from all subjects for immunogenicity testing (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 Enrollment log. If the individual is determined to be eligible for the study, he/she will be enrolled into the study.

5.1.3 Enrollment

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

5.1.4 Randomization

Enrolled subjects will be randomized in the IRT system and automatically assigned a unique Subject ID. 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. After randomization, the Screening Number ceases to be used and remains in the Screening and Enrollment Log only. The list of randomization assignments is produced by the IRT service provider and approved by Seqirus or delegate.

Subjects will be randomized in a 2:1:1 ratio to aQIV, aTIV-1, and aTIV-2.

If for any reason, after signing the informed consent form (ICF), the subject who is eligible and enrolled 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 Enrollment 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.

5.2 Vaccination Clinic Visit(s)

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 **must** be taken prior to vaccination.

After completing the prevaccination procedures as described in Section 5.1, Prevaccination Clinic Visit(s), the vaccine will be administered to the subject according to

the procedures described in Section 6.3, Vaccine Preparation and Administration. Prior to administration of each vaccination, it should be confirmed that the subject is eligible for vaccination and does not meet any criteria for delaying study vaccination as described in Section 4, Selection of Study Population.

5.2.1 Postvaccination Procedures

The following postvaccination 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 the ruler provided, how to measure local solicited adverse events, and how to report systemic solicited 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.

Diary Card Training

A Diary Card will be used in this study to document solicited adverse events from Day 1 to Day 7. The Diary Card is the only source for collection of these data; therefore, it is critical that the subject completes the Diary Card correctly. The subject should be trained on how and when to complete each field of the Diary Card. The Diary Card should be completed on a daily basis, preferably in the evening, 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 representative should be trained on how to self-measure local solicited adverse events and body temperature. The measurement of solicited local adverse events is to be performed using the ruler provided by the site.

The subject or legal representative should be instructed how to perform body temperature measurement using the thermometer provided by the site. Temperature should be checked at least daily; if the subject feels unusually hot or cold during the day, the subject or legal representative should make additional measurement of body temperature. If the subject has fever, the highest body temperature observed that day should be recorded in the Diary Card.

Diary Card training should be directed at the individual(s) who will perform the measurements of adverse events and who will enter the information into the Diary Card. In some situations, the Diary Card may be completed by somebody other than the subject or legal representative (except study site personnel). If a person other than the subject or legal representative enters information into the Diary Card, the reason that the subject cannot complete their own Diary Card and the person's identity and relationship to the

subject must be documented in the Diary Card. Any individual that makes entries into the Diary Card must receive training on completion of the Diary Card at the time of the visit. This training must be documented in the subject's source.

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

Plan Next Study Activities

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

Discharge

The subject or legal representative 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.

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

5.2.2 Postvaccination Reminder Call

Reminder calls are not intended to be an interview for collection of safety data. If the subject wishes to describe safety information, this information should only be collected by a qualified healthcare professional at the site, and the safety data described must be written down in the subject's source documentation and CRF.

Diary Card Day 3 Reminder Phone Call

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

5.3 Postvaccination Clinic Visit and Safety Calls

A postvaccination clinic visit will be performed on Day 22. Postvaccination Safety Calls will be performed on Day 15, Day 91, and Day 181.

5.3.1 Follow-up Clinic Visit

At the clinic visit on Day 22, the Diary Card will be reviewed and collected. No changes to the information recorded within the Diary Card are permissible. For details on the Diary Card see Section 3.4.2, Tools Used for Data Collection and Section 5.2.1, Postvaccination Procedures. The subject or legal representative 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 qualified 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 representative 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 Day 22 clinic visit, the subject will be asked 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 the Day 22 clinic visit, 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 the Day 22 clinic visit, 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 CRF(s).

During the Day 22 follow-up clinic visit, approximately 10 ml of blood will be drawn (see Section 3.5, Collection of Clinical Specimens).

The site should also schedule the next study activity, the Day 91 safety call, with the subject. It is recommended for the site to also schedule in the remaining upcoming study activities whenever possible.

At the Day 22 follow-up clinic visit, the subject will receive a written reminder of the next planned study activity. The subject or legal representative 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 is otherwise of concern.

5.3.2 Safety Follow-up Phone Calls

Safety follow-up calls will be performed on Day 15, Day 91, and Day 181.

Safety follow-up calls are calls made to the subject by a qualified healthcare professional designated on the site delegation log. These calls will follow a script which will facilitate the collection of relevant safety information. The subject 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 181 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), 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.

On Day 15, if the subject reports during the phone contact that symptoms are present 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.

On Day 15, the subject will be reminded to contact the site immediately if the subject experiences symptoms meeting 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.

The subject will receive a reminder of the next planned study activity. The subject 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.

5.4 Unscheduled Visits

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 Influenza-Like-Illness Criteria

Clinic Visit – Obtaining NP Swab

Subjects will be asked to come to the site for an unscheduled clinic visit when experiencing symptoms meeting the ILI criteria from Day 1 through Day 22. 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 record 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 and related information, in the source documents and in the CRF (ILI-report and adverse events section)
- Schedule next study activity

5.5 Study Termination Phone Call

The study termination visit (call) will occur on Day 181. The termination visit will 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 CRF 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.

The termination telephone call 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), 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.

The site will complete the termination CRF 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. Early Termination Visits include subjects who were randomized but not treated.

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 the Diary Card, if applicable
- Review the subject's safety data (if collection of these was in progress at the time of study termination)

The site will complete the termination CRF 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 Vaccines

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. All three influenza vaccines are made similarly, with the exception of the influenza strains included.

Investigational Vaccine: aQIV

An approximately 0.5 mL dose of aQIV (quadrivalent MF59C.1 adjuvanted influenza vaccine) contains nominally 15 mcg of hemagglutinin (HA) of each of the 2 influenza type A strains and each of the 2 influenza type B strains for a total of 60 mcg of HA in the vaccine. The strain composition is that recommended by the World Health Organization for the 2017-2018 Northern Hemisphere influenza season (WHO, 2017) for quadrivalent vaccines. 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 Hemagglutinin (HA) and neuraminidase (NA) antigens from the influenza virus strains recommended by WHO for the manufacture of influenza vaccine for 2017-2018 season A/ Michigan/45/2015 (H1N1) A/ Hong Kong/4801/2014 (H3N2) B/ Phuket/3073/2013 (Yamagata lineage) B/ Brisbane/60/2008 (Victoria lineage)	nominally 15mcg HA/strain	Active ingredient

Names of Ingredients	Quantity per dose*	Function
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
Other Ingredients		
Sodium chloride	4.00mg	Isotonic aid
Potassium chloride	0.10mg	Buffer
Potassium dihydrogen phosphate	0.10mg	Buffer
Disodium phosphate dehydrate	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	Prefilled syringe	

* the quantities indicated in this table reflect the amount in a 0.5 mL dose.
** residues of special relevance: barium sulfate, cetyltrimethylammonium bromide (CTAB), chicken proteins, such as ovalbumin, formaldehyde, kanamycin and neomycin sulfate.

US-licensed Comparator Vaccine: Fluad, aTIV-1

An approximately 0.5 mL dose of aTIV-1 (trivalent MF59C.1 adjuvanted influenza vaccine) contains nominally 15 mcg of hemagglutinin (HA) of each of the 2 influenza type A strains and one influenza type B strain for a total of 45 mcg of HA in the vaccine. The strain composition is that recommended by the World Health Organization for the 2017-2018 Northern Hemisphere influenza season (WHO, 2017) for trivalent vaccines. The full composition of the vaccine is reported in Table 6.1-2.

Table 6.1-2: aTIV-1 Vaccine Composition

Names of Ingredients	Quantity per dose*	Function
Active Ingredients Hemagglutinin (HA) and neuraminidase (NA) antigens from the influenza virus strains recommended by WHO for the manufacture of influenza vaccine for 2017-2018 season A/ Michigan/45/2015 (H1N1) A/ Hong Kong/4801/2014 (H3N2) B/ Brisbane/60/2008 (Victoria lineage)	nominally 15mcg 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
Other Ingredients		
Sodium chloride	4.00mg	Isotonic aid
Potassium chloride	0.10mg	Buffer
Potassium dihydrogen phosphate	0.10mg	Buffer
Disodium phosphate dehydrate	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	Prefilled syringe	

* the quantities indicated in this table reflect the amount in a 0.5 mL dose.
** residues of special relevance: barium sulfate, cetyltrimethylammonium bromide (CTAB), chicken proteins, such as ovalbumin, formaldehyde, kanamycin and neomycin sulfate.

Comparator Vaccine Containing the Alternate B strain: aTIV-2

An approximately 0.5 mL dose of aTIV-2 (a trivalent MF59C.1 adjuvanted influenza vaccine) contains nominally 15 mcg of hemagglutinin (HA) of each of the 2 influenza type A strains and one influenza type B strain for a total of 45 mcg of HA in the vaccine. The strain composition is that recommended by the World Health Organization for the 2017-2018 Northern Hemisphere influenza season (WHO, 2017) for trivalent vaccines. for the A strains, but the one B strain included in this vaccine is the second influenza B strain recommended for inclusion in quadrivalent vaccines (ie, the alternate B strain). The full composition of the vaccine is reported in Table 6.1-3.

Table 6.1-3: aTIV-2 Vaccine Composition

Names of Ingredients	Quantity per dose*	Function
Active Ingredients Hemagglutinin (HA) and neuraminidase (NA) antigens from the influenza virus strains recommended by WHO for the manufacture of influenza vaccine for 2017-2018 season A/ Michigan/45/2015 (H1N1) A/ Hong Kong/4801/2014 (H3N2) B/ Phuket/3073/2013 (Yamagata lineage)	nominally 15mcg 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
Other Ingredients		
Sodium chloride	4.00mg	Isotonic aid
Potassium chloride	0.10mg	Buffer
Potassium dihydrogen phosphate	0.10mg	Buffer
Disodium phosphate dehydrate	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	Prefilled syringe	

* the quantities indicated in this table reflect the amount in a 0.5 mL dose
** residues of special relevance: barium sulfate, cetyltrimethylammonium bromide (CTAB), chicken proteins, such as ovalbumin, formaldehyde, kanamycin and neomycin sulfate

6.2 Non-Study Vaccines

Not applicable.

6.3 Vaccine Preparation and Administration

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 and the Pharmacy Manual. All vaccines will be administered only by personnel who are qualified to perform that function under applicable local laws and regulations for the specific study site.

Detailed vaccine preparation and administration instructions will be provided to investigators 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 vaccination prior to first study vaccine administration is determined by evaluating the entry criteria outlined in protocol Section 4.1, Inclusion Criteria and Section 4.2, Exclusion Criteria.

Eligibility for 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.

Standard immunization 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 or intragluteally**.

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 is administered in one dose

of study vaccine. An administration error includes underdosing, where an incomplete dose of vaccine is given, caused by mechanical failure or other reason.

An overdose would also occur if two doses of the study vaccine are administered within half the time of the recommended interval between doses, as defined in the protocol.

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 serious adverse event, it must be reported as such within 24 hours to the Sponsor or delegate.

6.5 Prior and Concomitant Medications and Vaccines

All influenza vaccination history in the 5 years prior to subject enrollment 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 enrollment (or for the 2016 – 2017 flu season) into the study should additionally be recorded on the Prior and Concomitant Medications CRF.

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 CRF. Any blood products received within 3 months prior to enrollment must also be documented in the Prior and Concomitant Medications CRF. Vitamins and minerals are excluded from this scope.

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 CRF. 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 low-dose aspirin for cardiovascular prophylaxis is not considered effective analgesic therapy and is thus allowed.

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 enrollment.

Administration of any other influenza vaccine, seasonal or pandemic, is prohibited until after collection of the follow-up serology on Day 22.

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

- All concomitant medications from Day 1 to Day 22
- All medications associated with SAEs, NOCD, AESIs, and AEs that lead to premature withdrawal from the study, from Day 1 to study termination
- All vaccines, including any seasonal or pandemic influenza vaccines, from Day 1 to Day 181

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.

Use of the following concomitant medications after enrollment and prior to the Day 22 blood collection should be documented on the Concomitant Medication CRF page as they may have an effect on the interpretation of the study objectives and therefore may be determined to be a reason for exclusion from one of the analysis sets.

- Anti-viral medication following ILI, prior to obtaining a NP swab
- Blood, blood products or a parenteral immunoglobulin preparation
- Oral or systemic corticosteroids (topical, inhaled, intranasal corticosteroids are permitted)
- Other immunosuppressive agents

6.6 Vaccine Supply, Labeling, Storage and Tracking

The Sponsor will ensure the following:

- Supply the study vaccines
- 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:
  - No 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 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 or terminates the study early (whichever comes first). AEs occurring after the informed consent form 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 listed 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 the subject or legal representative(s) for 7 consecutive days, using a predefined Diary Card.

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

Solicited Local Adverse Events

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

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/100.4°F, as measured preferably orally.

The study staff must review the data entered into the Diary Card 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 serious adverse event (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 Diary Card and that was spontaneously communicated by a subject or legal representative(s) who has signed the informed consent.

All unsolicited adverse events, and medications used to treat them, will be collected from study admission (at the time of informed consent) through the Day 22 clinic visit. After the day 22 visit, only unsolicited adverse events, and medication used to treat them, which meet criteria for the following will be collected: serious adverse events, adverse events of special interest, new onset of chronic disease, and events leading to study discontinuation.

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 coexistence 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 is a new diagnosis of a chronic medical condition that was not present or suspected prior to study enrollment
- AEs leading to withdrawal: adverse events leading to study withdrawal

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

When the subject or legal representative(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 AEs 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 serious adverse event (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 (ie, 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 serious adverse event need not, by definition, be severe.

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 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.

SAEs will be evaluated by Seqirus or its 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.

Any 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 (eg, 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.

7.1.5 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 AESIs 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 EDC along with any medication used to treat the condition.

Onset of an AESI is to be reported to Seqirus or its designee via EDC in the same manner and time frame as an SAE (see Section 7.1.6 and SAE/AESI Reporting Plan).

All AESIs will be reviewed for signal evaluation by Seqirus or its designee and assessed for expedited reporting.

7.1.6 Methods for Recording and Reporting 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. All findings in subjects experiencing AEs must also be reported in the subject's source document.

All SAEs and AESIs 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 via EDC. If entry into EDC is not possible (eg, because the system is non-functional), the paper SAE/AESI Form must be completed and submitted via facsimile/email to Seqirus or its designee. Refer to SAE/AESI Reporting Plan for specific instructions and contact details for collecting and reporting SAEs.

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 reporting, 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.

7.1.6.1 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. There is no time limit on reporting for SAEs related to study vaccine. Instructions and contact details for collecting and reporting these suspected SAEs will be provided to the Investigator.

7.1.7 Pregnancies

Not applicable for this study.

7.1.8 Safety Laboratory Measurements

No scheduled safety laboratory measurements are planned for this study.

7.2 Efficacy Assessment

Not applicable.

7.3 Immunogenicity Assessment

The measure of immunogenicity used in this study, hemagglutination inhibition (HI) is widely accepted and generally recognized as reliable, accurate, and relevant (able to describe the quality and extent of the immune response).

The immunogenicity analyses will evaluate immunogenicity of aQIV and the comparator aTIVs measured by the HI assay by titrating antibodies against homologous or heterologous influenza strains. Homologous strains are antigenically similar to the strains in the vaccine and heterologous are antigenically distinct (CDC, 2014).

Additional immunologic assays, including microneutralization, may be used to measure neutralizing antibodies.

Testing will be conducted by Seqirus designated qualified laboratory personnel blinded to the treatment assignment and the visit. Please see the Protocol Ancillary Document for name(s) and details.

8. STATISTICAL CONSIDERATIONS

8.1 Endpoints

8.1.1 Primary Endpoints

8.1.1.1 Co-Primary Immunogenicity Endpoints

The immunogenicity of study vaccines will be assessed 21 (i.e., on Day 22) days after vaccine administration by measuring the hemagglutination inhibition (HI) antibody titers to the four virus strains included in the vaccines.

The noninferiority of aQIV compared to aTIV-1, and to aTIV-2 will be assessed for the eight co-primary endpoints of HI geometric mean titer (GMT) and seroconversion rate (SCR) for each virus strain included in the vaccines as follows:

- The GMT ratio* for the A/H1N1 strain
- The GMT ratio for the A/H3N2 strain
- The GMT ratio for the B strain (Yamagata lineage)
- The GMT ratio for the B strain (Victoria lineage)
- The difference between the SCR**for the A/H1N1 strain
- The difference between the SCR for the A/H3N2 strain
- The difference between the SCR for the B strain (Yamagata lineage)
- The difference between the SCR for the B strain (Victoria lineage)

Immunogenicity results obtained from aTIV-1 and aTIV-2 for both A/H1N1 and A/H3N2 strains will be pooled for comparison with aQIV.

**The GMT ratio is defined as the geometric mean of the post-vaccination (Day 22) HI titer for aTIV-1 (or aTIV-2) over the geometric mean of postvaccination (Day 22) HI titer for aQIV.*

***The SCR is defined as the percentage of subjects with either a prevaccination HI titer < 1:10 and a post-vaccination HI titer ≥ 1: 40 or a prevaccination HI titer ≥ 1:10 and a ≥ 4-fold increase in postvaccination HI titer.*

The second co-primary immunogenicity objective for aQIV will be assessed 21 days after vaccine administration by applying CBER criteria for the elderly population for each of the 4 strains included in aQIV:

- The percent of subjects achieving seroconversion for HI antibody

- The percent of subjects achieving an HI antibody titer ≥ 1:40

The study is considered successful if the (16) co-primary endpoints are achieved.

8.1.2 Secondary Immunogenicity Endpoints

- The measures of immunogenicity of aQIV, aTIV-1 and aTIV-2 used for Secondary objective 1 as determined by the HI assay against homologous strains at Day 1 and 22 (unless indicated otherwise), include the following:
  - GMT: Geometric mean of HI titers on Day 1 and Day 22
  - Geometric mean ratio (GMR)*: The geometric mean of the fold increase of post- vaccination HI titer over the pre-vaccination HI titer (Day 22/Day 1)
  - The percentage of subjects with a titer ≥40 at Day 1 and Day 22
  - SCR: the percentage of subjects with either a prevaccination HI titer < 1:10 and a postvaccination HI titer ≥ 1:40 or a prevaccination titer ≥ 1:10 and a ≥ 4-fold increase in postvaccination titer on Day 22

- For Secondary objective 2, the immunologic superiority of HI antibody responses for the alternate B strain (the influenza B strain included in the aQIV but not in the aTIV formulation) in aQIV will be assessed for each aTIV separately, using the endpoints of the ratio of HI GMT and the difference of SCR for each B virus strain 21 days after vaccination.

8.1.3 Secondary Safety Endpoints

Safety and tolerability will be assessed by the frequency and severity of:

- Solicited local and systemic adverse events (AEs) for 7 days following vaccination (Day 1 through Day 7)
- All unsolicited AEs for 21 days following vaccination (Day 1 through Day 22) and medication associated with these events
- Serious AEs (SAEs), AEs leading to withdrawal from the study, new onset of chronic diseases (NOCDs), AEs of special interest (AESIs), and concomitant medications associated with these events as collected from Day 1 through Day 181

8.1.4 Exploratory Immunogenicity Endpoints

- Exploratory immunogenicity endpoints include:
- GMTs: Geometric mean HI titers (GMTs) at Day 1 and Day 22
- SCRs: Percentage of subjects with either a prevaccination HI titer < 1:10 and a postvaccination HI titer ≥ 1:40, or a prevaccination titer ≥ 1:10 and a ≥ 4-fold increase in postvaccination titer at Day 22.
- In case of any additional optional immunogenicity analyses, such as MN, or assessments using heterologous influenza strains, the immune response will be characterized in a similar manner as described in the secondary immunogenicity endpoints section above.

Further details regarding the endpoints and analyses of these assays will be described in the Statistical Analysis Plan (SAP) prior to unblinding.

8.2 Success Criteria

The study is considered successful if the co-primary objectives are achieved.

8.2.1 Success Criteria for Co-Primary Endpoints

8.2.1.1 *To demonstrate noninferiority*

In line with the FDA Guidance on seasonal inactivated influenza vaccines (Guidance for Industry Clinical Data Needed to Support Licensure of Seasonal Inactivated Influenza Vaccines 2007), aQIV will be considered to be noninferior to aTIV-1, containing the same virus strains as the US licensed adjuvanted trivalent influenza vaccine, and aTIV-2, containing the alternate B strain if, for each of the four strains, the following statistical criteria are met:

- The upper bound of the two-sided 95% confidence interval (CI) for the ratio of the GMTs does not exceed 1.5. The GMT ratio will be calculated as GMT $_{aTIV}$/GMT $_{aQIV}$; and
- The upper bound of the two-sided 95% CI for the difference between the SCRs does not exceed 10%. The difference in SCRs will be calculated as Seroconversion $_{aTIV}$–Seroconversion $_{aQIV}$

8.2.1.2 *CBER criteria for Co-Primary Endpoints:*

The endpoints for percent of subjects vaccinated with aQIV 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 (FDA, 2007):

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

The statistical evaluation consists of the observed proportion together with the corresponding two-sided 95% CI per strain. No adjustment for type I error for multiplicity is made.

No adjustment for type I error for multiplicity will be made. The study is successful if the co-primary immunogenicity objectives are achieved.

8.2.2 Success Criteria for Secondary Objectives

8.2.2.1 Success Criteria for Secondary Immunogenicity Endpoints

There are no specific success criteria for the assessment of immunoassay results (first secondary objective).

Superiority of aQIV versus aTIV-1 and aTIV-2 for the alternate B strain will be assessed using the GMT ratio (GMT_{aTIV}/GMT_{aQIV}) and difference in SCR ($SCR_{aTIV} - SCR_{aQIV}$) at Day 22. Point estimates and two-sided 95% CIs will be obtained as described for the primary endpoint. Superiority will be declared if the upper limit of the two-sided 95% CI for the difference in $SCR_{aTIV} - SCR_{aQIV)}$ is < 0%, and the upper limit of the two-sided 95% CI for the GMT ratio (GMT_{aTIV} / GMT_{aQIV}) is < 1 for both B strains.

8.3 Description of Analysis Sets

There will be four analysis populations defined for the study analyses. These are defined in more detail in the SAP.

8.3.1 All Enrolled Set

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

8.3.2 Full Analysis Set

All subjects in the All Enrolled Set who are randomized and receive a study vaccination. The FAS will be used to produce summaries and listings of subject characteristics.

8.3.3 Safety Set

The Safety Set will comprise all subjects in the FAS who received at least one dose or partial dose of Study Vaccine and have provided any evaluable follow-up safety data. The safety set will be used to produce summaries and listings of all safety data.

8.3.4 Evaluable Set – Immunogenicity Analysis

The Evaluable Set for immunogenicity analyses will comprise all subjects in the FAS who:

- receive vaccine on Day 1
- provide serology specimens which yield valid serology assay results from both Day 1 and Day 22
- do not experience a laboratory-confirmed influenza illness between Day 1 and Day 22, and
- do not receive any prohibited medication during the study that is medically assessed to potentially impact immunogenicity results

8.3.5 Per-Protocol Set

The Per-Protocol Set (PPS) will comprise all subjects in the Evaluable Set who do not have any protocol deviations that are medically assessed as potentially impacting on immunogenicity results.

The Per Protocol Set will be the primary population of interest for the primary/secondary immunogenicity analysis and a supporting analysis will be performed using the Evaluable Set. Membership of the PPS will be determined prior to unblinding the study.

Duplicate tables of primary and secondary immunogenicity analyses may also be produced based on the Evaluable population if there is >1% difference in the total number of subjects between the Per-Protocol Population and the Evaluable Population. The decision to produce tables based on the Evaluable Population will be made by Seqirus after population sets are finalised and prior to unblinding.

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 is unblinded during the study, except for SUSAR, he/she will be excluded from the PPS.

8.3.6 Subgroups

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

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

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 enrollment (≥65-74, ≥75-84, and ≥85years)
- Sex
- Race

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. Major protocol deviations will be defined as exclusionary from the analysis according to protocol objectives and endpoints, which will be specified in the statistical analysis plan. In some cases, exclusion of data may be due to a reason other than a protocol deviation, e.g. early termination.

Any deviation that affects the subject's rights, safety, or well- being and/or the completeness, accuracy and reliability of the study data constitutes a major protocol deviation. Changes or alterations in the conduct of the trial which do not have a major

impact on the subject's rights, safety or well-being, or the completeness, accuracy and reliability of the study data are not considered major protocol deviations. All deviations will be reviewed to determine the final list of deviations that will be used for exclusion from the analysis set(s). This will be defined in the statistical analysis plan prior to unblinding.

All protocol deviations will be classified into those which are major and those which are not. Major protocol deviations will be summarized by vaccine, center (overall) and grouped into the different categories as defined above. The site monitor will keep the investigator informed of all protocol deviations, so that the investigator can comply with reporting these deviations to the local EC/IRB according to their institutional policy. Prior to unblinding, designated staff at the Sponsor will develop a memo that describes the selected deviations that are identified as exclusions from analysis populations. This memo will be included in the trial master file.

8.4 Statistical Analysis Plan

A complete description of the statistical analyses and methods will be available in the Statistical Analysis Plan (SAP), which will be finalized prior to unblinding.

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 enrollment will be calculated overall and by vaccine groups.

Distributions of subjects by sex, ethnic origin (race, ethnicity), and previous vaccination status will be summarized overall, and by vaccine group.

8.4.1.1 Concomitant Medications

Use of concomitant medication will be presented by treatment, age cohort, therapeutic area, and preferred drug name.

Concomitant medications are all medications taken during the study period, including those started before but ongoing at vaccination.

If a start date for a medication is partially or fully missing, and it is unclear as to whether the medication is prior or concomitant, it will be assumed that it is concomitant.

Medications will be coded using the WHO Drug dictionary.

8.4.2 Analysis of Primary Objective(s)

8.4.2.1 Analysis of Primary Efficacy Objective(s)

Not Applicable.

8.4.2.2 Analysis of Co-Primary Immunogenicity Objectives

The co-primary immunogenicity objectives are:

1. To demonstrate that vaccination with aQIV elicits an immune response that is not inferior to that of an aTIV containing the same virus strains as the US licensed adjuvanted influenza vaccine (Fluad, aTIV-1), and an aTIV containing the alternate B strain (aTIV-2) among adults ≥65 years of age
2. To assess the immunogenicity of aQIV in adults ≥65 years of age, based on CBER (Center for Biologics Evaluation and Research) criteria

8.4.2.2.1 Statistical Hypotheses

Noninferiority of aQIV to aTIV-1 and aTIV-2

To demonstrate that vaccination with aQIV elicits an immune response that is not inferior to that of an aTIV containing the same virus strains as the US licensed adjuvanted influenza vaccine (Fluad, aTIV-1), and an aTIV containing the alternate B strain (aTIV-2) among adults ≥65 years of age. according to the FDA Guidance on seasonal inactivated influenza vaccines *(Guidance for Industry Clinical Data Needed to Support Licensure of Seasonal Inactivated Influenza Vaccines 2007)*.

aQIV will be considered to be noninferior to aTIV if, for each of the four strains, the following statistical criteria are met:

- The upper bound of the two-sided 95% CI for the ratio of the GMTs does not exceed 1.5. The GMT ratio will be calculated by $GMT_{aTIV/}$ GMT_{aQIV}
- The upper bound of the two-sided 95% CI for the difference between the SCRs does not exceed 10%. The difference in SCR will be calculated by $SCR_{aTIV} - SCR_{aQIV}$

In mathematical notation, the statistical hypotheses to be tested for the primary immunogenicity analysis correspond to:

H0: $GMTri > 1.5$, for any strain

Ha: $GMTri \leq 1.5$, for all strain

and

H0: $Di > 10$, for any strain

Ha: $Di \leq 10$, for all strain

where *GMTri* is any of the 4 strain-specific post immunogenicity dose GMT ratios namely,

- $GMT_{aTIV\text{-}1/}$ GMT_{aQIV} for B/Yamagata strain
- $GMT_{aTIV\text{-}2/}$ GMT_{aQIV} for B/Victoria strain
- Pooled $GMT_{(aTIV\text{-}1}$ and $_{aTIV\text{-}2)}$ /GMT_{aQIV} for A/H1N1 strain
- Pooled $GMT_{(aTIV\text{-}1}$ and $_{aTIV\text{-}2)}$ /GMT_{aQIV} for A/H3N2 strain

and *Di* is the 4 strain-specific post dose SCRs ($\pi_{aTIV\text{-}1}$, $\pi_{aTIV\text{-}2,}$ π_{aQIV}) difference, namely,

- $\pi_{aTIV\text{-}1} - \pi_{aQIV}$ for B/Yamagata strain
- $\pi_{aTIV\text{-}2} - \pi_{aQIV}$ for B/Victoria strain
- Pooled $\pi_{(aTIV\text{-}1}$ and $_{aTIV\text{-}2)}$-π_{aQIV} for A/H1N1 strain
- Pooled $\pi_{(aTIV\text{-}1}$ and $_{aTIV\text{-}2)}$-π_{aQIV} for A/H3N2 strain

where π_v denotes the seroconversion rates for the *v*th vaccine (aQIV, aTIV-1, aTIV-2).

CBER Immunogenicity Criteria

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 (FDA, 2007):

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

Assuming that $Y_{jk} \sim B(1, \pi_k)$, $Z_{jk} \sim B(1, \tau_k)$, j=1,..,n, identical and independent Bernoulli distributed random variables with π_k representing the unknown SC proportion postvaccination and τ_k representing the unknown SP (seroprotection, titer ≥ 1:40) proportion postvaccination in aQIV for strain k, where k denotes the 4 strains contained in aQIV vaccines, CBER requirements for the aQIV vaccine group translate into following hypothesis

$$H_{0k}^{(SC)}: \pi_k \leq 0.3 \qquad \text{vs} \qquad H_{1k}^{(SC)}: \pi_k > 0.3$$

$H_{0k}^{(SP)}$: $\tau_k \leq 0.6$ vs $H_{1k}^{(SP)}$: $\tau_k > 0.6$

All hypotheses related to CBER criteria will be tested on unadjusted 5% significance levels.

8.4.2.2.2 Analysis Sets

The Per Protocol Set will be used for the primary immunogenicity analysis and a supporting analysis will be performed using the Evaluable Set, as noted in Section 8.3.4. Evaluable Set – Immunogenicity Analysis. Duplicate tables of primary and secondary immunogenicity analyses may also be produced based on the Evaluable population if there is >1% difference in the total number of subjects between the Per-Protocol Population and the Evaluable Population.

8.4.2.2.3 Statistical Methods

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

Co-primary immunogenicity endpoints of GMT and SCR for each virus strain contained in the vaccine will be assessed for subjects ≥ 65 years overall. For A/H1N1 and A/H3N2 strains the two aTIV groups will be pooled.

Primary analysis will be performed for subjects ≥ 65 years for the Per-Protocol Set. The difference in SCRs will be presented with exact 95% (CIs). Each of the four strains will be analyzed separately.

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

To determine the GMT ratio (adjusted analysis) a general linear model (GLM) will be fitted on log transformed (base ten) post-vaccination HI titer as the outcome variable and terms for covariates: vaccine treatment, pre-vaccination HI titer, age stratum, gender, vaccination history, age-by-vaccine interaction and study site. Potential covariate interaction effects will also be examined in the fit of the GLM. From the model, an adjusted difference in least square means (on the log scale) will be produced with 95% confidence limits. The estimated difference and the confidence limits will be back transformed to obtain an *adjusted GMT ratio* with 95% confidence limits. Each of the four strains will be analyzed separately. The adjusted GMT ratio will be the result for which the non-inferiority assessment of the HI GMT co-primary endpoint will be based on.

The statistical models might be reduced in case they fail to converge. Further details will be provided in the Statistical Analysis Plan.

The complete set of covariates that may be used in the model to calculate the adjusted GMT ratio will include treatment group (3 treatments), age sub-group (3 categories, (≥65-74, ≥75-84, and ≥85years), sex (male or female), influenza vaccination received prior year (Y or N), prevaccination mean GMT titer (value) and investigator site (site identifier)

The GLM specification is: Adjusted Analysis GMT Model: Log-transformed Post-vaccination HI Titer = Vaccine + Age Strata + Gender + Vaccination History [y/n] + Log-transformed Prevaccination HI Titer + Site + Age Strata*Vaccine.

For any strain, the interaction term *Age Strata*Vaccine* will be removed from the fit of the model if it is assessed to be not significant.

The measure of the *unadjusted* GMT ratio based on post-vaccination GMTs only will also be presented.

In line with the FDA Guidance on seasonal inactivated influenza vaccines *(Guidance for Industry Clinical Data Needed to Support Licensure of Seasonal Inactivated Influenza Vaccines 2007)*. aQIV will be considered to be noninferior to aTIV if, for each of the four strains, the following statistical criteria are met:

- The upper bound of the two-sided 95% Confidence Interval (CI) for the ratio of the GMTs does not exceed 1.5. The GMT ratio will be calculated by $GMT_{aTIV/}$ GMT_{aQIV}
- The upper bound of the two-sided 95% CI for the difference between the SCRs does not exceed 10%. The difference in SCR will be calculated by $\pi_{aTIV} - \pi_{aQIV}$

To achieve the CBER criteria:

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

Binary data (ie, percentages of subjects with seroconversion and with titer ≥ 1:40) will be summarized for each group using unadjusted estimates and will be reported together with two-sided exact 95% CIs. No multiplicity adjustment to the CI levels will be implemented.

Handling of missing values for Immunogenicity Data:

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

8.4.3 Analysis of Secondary Objective(s)

8.4.3.1 Analysis of Secondary Safety Objective(s)

Not applicable.

8.4.3.2 Analysis of Secondary Efficacy Objective(s)

Not applicable.

8.4.3.3 Analysis of Secondary Immunogenicity Objective(s)

Characterization of immunogenicity of aQIV, aTIV-1 and aTIV-2:

The measures of immunogenicity of aQIV, aTIV-1 and aTIV-2 will be assessed in terms of HI antibodies. Serum HI antibody titers against the 4 influenza vaccine strains will be used to calculate:

- GMT: Geometric mean of HI titers on Day 1 and Day 22
- GMR: The geometric mean of the fold increase of post- vaccination HI titer over the pre-vaccination HI titer (Day 22/Day 1)
- The percentage of subjects with a titer ≥ 1:40 at Day 1 and Day 22
- SCR: the percentage of subjects with either a prevaccination HI titer < 1:10 and a postvaccination HI titer ≥ 1:40 or a prevaccination titer ≥ 1:10 and a ≥ 4-fold increase in postvaccination titer on Day 22

Superiority of immunologic response for aQIV vs aTIV:

Superiority of aQIV over aTIV-1 and aTIV-2 for antibody response to the alternate B strain will be assessed using the GMT ratio (GMT_{aTIV}/GMT_{aQIV}) and difference in SCR

($SCR_{aTIV} - SCR_{aQIV}$) at Day 22. Point estimates and 95% confidence limits will be obtained as described for the primary endpoint. Superiority will be declared if the upper limit of the two-sided 95% CI for the difference in $SCR_{aTIV} - SCR_{aQIV}$) is < 0 and the upper limit of the two-sided 95% CI for the GMT ratio (GMT_{aTIV}/GMT_{aQIV}) is < 1 for both B strains.

8.4.3.3.1 Statistical Hypotheses

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

Superiority of B-strain response (geometric mean titers and proportions of subjects with seroconversion):

For superiority of aQIV B strain response, the hypotheses are that immunologically aQIV is superior compared to aTIV-1 and aTIV-2 for the B strain that is not included in each TIV vaccine separately. In mathematical form, these are:

$$H_{0k}^{(GMT)}: GMTr_k \geq 1 \text{ vs } H_{1k}^{(GMT)} GMTr_k < 1 \text{ for } k=1,2$$

and

$$H_{0k}^{(SCR)}: D_k \geq 0 \text{ vs } H_{1k}^{(SCR)} D_k < 0 \text{ for } k=1,2$$

where $GMTr_k$ is the ratio of geometric mean titer $GMT_{aTIV\text{-}k}/GMT_{aQIV}$ of mismatched B strain for k=1, 2, and D_k is the differences $\pi_{aTIV\text{-}k} - \pi_{\backslash aQIV}$ of mismatched B strain Day 22 SCR differences for k=1,2.

8.4.3.3.2 Analysis Sets

The secondary objective superiority testing will be performed using the Per Protocol Set (PPS).

8.4.3.3.3 Statistical Methods

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

Unadjusted for GMTs, GMRs and pertaining two-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 (ie, 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 exact 95% CIs. 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), ie, not informative. Therefore, the key secondary analysis will comprise a complete case analysis only, without introducing any bias. Imputation methods will not be used.

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

8.4.4 Secondary Safety Objective

8.4.4.1 Analysis of Extent of Exposure

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

8.4.4.2 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.

Postvaccination 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 definitions 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” categories. For the definition of severity grades please refer to Section 7.1.1, Solicited Adverse Events of the protocol.

Each solicited local and systemic adverse event will also be further summarized as “none” versus “any”. “Any” will include measurements 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 vaccine group will be provided. The influence of antipyretics and analgesics use on the occurrence of specific adverse events (e.g., fever, pain) may be assessed.

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 by 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.

8.4.4.3 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 MedDRA dictionary. The adverse events will then be grouped by MedDRA preferred terms into frequency tables according to system organ class.

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 system organ class and preferred term within system organ class (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:

- Serious adverse events
- Adverse events that are possibly or probably related to vaccine
- Adverse events of special interest
- New onset of chronic disease
- Adverse events leading to withdrawal
- Adverse events 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], and [Day 1-181].

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

8.4.4.4 Analysis of Safety Laboratory Values

Not applicable.

8.4.5 Analysis of Exploratory Objectives

The exploratory objectives are:

1. Additional optional objectives include characterization of the immunogenicity of aQIV using other immunological assays (e.g., virus neutralization [MN] or anti-neuraminidase antibody assays may be performed)
2. To explore the association between immune response after administration of aQIV or the aTIV-1, containing the same virus strains as the US-licensed adjuvanted trivalent influenza vaccine, or the aTIV-2 containing the alternate B strain by baseline characteristics.

Exploratory immunogenicity objective 1

Exploratory objectives related to the MN-assay, immune response to heterologous influenza strains, or different antigens will be evaluated using similar methods for log normal. binomial data, and GMT and SCR as described in the statistical method for primary and secondary immunogenicity analysis.

Exploratory immunogenicity objective 2

- GMTs: Geometric mean of HI titers prevaccination (Day 1) and at Study Exit Visit
- Percentage of subjects with four-fold rise

Analyses of the exploratory immunogenicity endpoints will be performed with adjustment for covariates including prevaccination titer, vaccination history, age and gender to evaluate the contribution of these factors to variations in the immune response. The covariate adjustment will be performed with all of the specified covariates in the general linear model.

The full model specification for the GMT titers will be:

Log-transformed Post-Vaccination HI Titer = Vaccine + Age Strata + Gender+ Vaccination History + Log-transformed Prevaccination HI Titer.

The full model specification for the SCR rates will be:

SCR = Vaccine + Age Strata + Gender + Vaccination History + Log-transformed Pre-vaccination HI titer

Seroconversion rates will be analyzed using a logistic regression model, and GMT titers will be log transformed (base 10) and analyzed with a general linear model. Pre-vaccination titers will be log transformed and entered as a continuous covariate. Vaccination history will be a categorical variable indicating whether or not an individual received an influenza vaccination in the previous year. If the proportion vaccinated in the previous year is close to 100% then this covariate may be omitted to avoid creating an unstable model. Age will be entered according to the predefined strata (≥65-74, ≥75-84, and ≥85years). For the logistic regressions, the odds ratios will be presented with 95% CIs for each effect in the model. For the GLM least square mean estimates for the GMT ratio will be presented with 95% confidence limits for each effect in the model.

Further details of the analysis of exploratory be provided in the SAP.

8.5 Sample Size and Power Considerations

aQIV will be tested against aTIV comparators. The treatment randomization ratio is 2:1:1 (aQIV: aTIV-1: aTIV-2). This study is powered to achieve 80% power to demonstrate noninferiority over 8 co-primary endpoints, seroconversion rates for 4 strains, GMT for 4 strains using a one-sided alpha of 0.025 for each comparison. No adjustment for multiple endpoints will be made.

For comparisons of SCR a noninferiority margin of 10% (aTIV – aQIV) will be employed. It is assumed that the SCRs for A/ H1N1, A/ H3N2 and B strains for TIV are 73%, 73% and 40% respectively. These estimates are based on the estimated SCR rates of historical data, namely study protocol V70_27. It has been assumed that there is no difference in terms of SCR between aQIV and aTIV for all strains. For comparison of the GMT ratio, a noninferiority of 1.5 (aTIV/aQIV) will be employed. It is assumed that there is no difference between aQIV and aTIV (i.e., a ratio of 1) and that the standard deviation of log (titer) is 1.2.

Under these assumptions, N evaluable = 800 in the aQIV group and 400 in each aTIV group providing 800 and 800 subjects receiving aQIV and aTIV respectively for comparisons of A strains, and 800 and 400 subjects receiving aQIV and aTIV respectively for comparisons of B strains. This provides a total N evaluable = 1600. These numbers provide 99.45% power to detect differences in SCR for each A strain and 91.29 % power for each B strain, providing overall 82.42% power for the 4 SCR tests.

For GMT ratio tests each A strain test will have 100% power and each B strain test will have 99.98% power, providing 99.96% power for the 4 GMT ratio tests and consequently 82.39% power for the 8 co-primary endpoints. Overall 1600 evaluable subjects will be required. Allowing for a 10% drop-out N=1778 subjects will be recruited (Sample size calculations were performed using PASS v12).

The immunogenicity was powered to meet the criteria prespecified in the CBER guidance for acceptable immunogenicity: namely,

- the lower bound of the two-sided 95% confidence interval for the percent of subjects achieving seroconversion should exceed 30%, and
- the lower bound of the two-sided 95% confidence interval for the percent of subject achieving HI antibody titer ≥ 40 should exceed 60%

With a sample size of N=800 (evaluable) subjects for the aQIV group if the population SCR for A/ H1N1, A/ H3N2 and B strains for TIV is 73%, 73% and 40% respectively then the probability of observing a seroconversion rate that is significantly greater than 30% is approximately 100% (for the A/H1N1), 100%for A/H3N2 and 100% (for the B-strains).

With a sample size of N=800 (evaluable) subjects for the aQIV group if the population SP rates for A/ H1N1, A/ H3N2 and B strains for TIV is 91%, 99% and 64.6% respectively (as observed in V70_27) then the probability of observing a SP rate that is significantly greater than 60% is approximately 100% (for the A/H1N1), 100% for A/H3N2 and 76.47% (for the B-strains).

Table 8.5-1 summarizes the list of all co-primary endpoints with strains, the planned noninferiority margin and underlying assumptions used for the sample size computations.

Table 8.5-1: Summary of Assumptions Used for Sample Size Calculations

NI comparison	**H1N1**	**H3N2**	**B strains**
Test significance level, alpha (1-sided)	2.50%	2.50%	2.50%
Noninferiority Margin for the SCR comparison (%)	10	10	10
Assumed true SCR	73%	73%	40%
Power for SCR comparison tests for	99.45%	99.45%	91.29%

each strain (%)			
Global Power for 4 SCR Endpoints	**82.42%**		
Noninferiority Margin for the GMT ratio	1.5	1.5	1.5
Common Standard Deviation of $\log_e$(titer)	1.2	1.2	1.2
Power for GMT ratio tests for each strain (%)	99.99%	99.99%	99.98%
Global Power for 4 GMT ratio Endpoints	**99.96%**		
Global Power for 8 Co-primary Endpoints	**82.39%**		
CBER Criteria	**H1N1**	**H3N2**	**B strains**
Test significance level, alpha (1-sided)	2.50%	2.50%	2.50%
Seroconversion Threshold	30%	30%	30%
Assumed true SCR	73%	73%	40%
Power for SCR	100%	100%	100%
Global Power for 4 SCR Endpoints	**100%**		
Threshold for Rate $\geq$ 1:40	60%	60%	60%
Assumed True Rate $\geq$ 1:40	91%	99%	64.6%
Power for Rate $\geq$ 1:40	100%	100%	76.47%
Global Power for 4 $\geq$ 1:40 Endpoints	**76.47%**		
Global Power for the Second 8 Co-	**76.47%**		

primary Endpoints (CBER Criteria)	

A safety database of N = 800 has a 95% chance of detecting AEs that occur at a rate of 1 in 267. With a single stratum of 800 participants, the probability of observing at least one event for events with population rates of 1 in 300, 1 in 200, and 1 in 100 are 93.1%, 98.2% and 100%, respectively.

8.6 Interim Analysis

No interim analysis is planned for this study.

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) standard operating procedures and applicable regulatory requirements (eg, FDA, EMA, and ICH guidelines).

Prior to enrollment 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 enrolled subject (see Section 8.3.1, All Enrolled Set for definition of enrolled subject). Documentation of screened but not enrolled 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 enrollment.

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 that 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 CRFs. If there are multiple sources of information (e.g., Diary Card, 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 CRF (AE CRF). The AE CRF must also capture which source(s) of information were used to determine the adverse event (e.g. subject recall, medical chart, Diary Card).

9.2 Study Monitoring, Auditing and Source Data Verification

Prior to enrollment of the first study subject, Seqirus or its designee (eg, 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 CRFs will be verified by checking the CRF entries against source documents in order to ensure data completeness and accuracy as required by the study protocol.

Data verification may also be performed through a centralized review of data (eg, 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 enrolled 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 enrolled 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 case report forms (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 (European Parliament, 1995) 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 will be retained for a period of 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 (CPMP, 2001). 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, as described in Section 5.1.1, Informed Consent. 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 representative 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 representative(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 representative(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 will provide to investigators a proposed informed consent form 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 after IRB/EC approval.

13.3 Responsibilities of the Investigator and IRB/EC

The protocol and the proposed informed consent form 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), and Integrated Addendum to ICH E6(R2): Guideline for Good Clinical Practice (ICH, 2016). A signed and dated statement that the protocol and informed consent have been approved by the IRB/EC must be given to Seqirus 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 representative), 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/favorable 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/favorable 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/favorable 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.

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APPENDIX 1: EXAMPLES OF PRE-EXISTING MEDICAL CONDITIONS FOR CALCULATION OF RISK SCORE

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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[redacted])

Title: Seqirus Clinical Medical Lead

Date: Thursday, 18 May 2017, 20:18 GMT

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