Phase IV Clinical Trial

STUDY PROTOCOL

TITLE	A single-arm, open-label, multi-center, phase IV trial to evaluate the reactogenicity, safety, and immunogenicity of quadrivalent seasonal influenza vaccine (*Fluarix Tetra*) in participants aged 65 years and older in India
STUDY DRUG(S)	*Fluarix Tetra*
PHASE OF DEVELOPMENT	Phase IV
VERSION	2.0 Draft: 10-APR-2023 Final: 05-May-2023 Amendment: 01
SPONSOR	GlaxoSmithKline Biologicals SA, Rixensart, Belgium
CONDUCTED BY	IQVIA Consulting and Information Services India Private Limited, 902, 9th floor, B-Wing, Supreme Business Park, Hiranandani Gardens, Powai, Mumbai – 400076

This protocol contains confidential information that should only be disclosed to those persons responsible for execution and organization of the study and on condition that all such persons agree not to further disseminate it.

TABLE OF CONTENTS

List of Tables

List of Figures

Investigator Signature Page

Study Title: A single-arm, open-label, multi-center, phase IV trial to evaluate the reactogenicity, safety, and immunogenicity of quadrivalent seasonal influenza vaccine (*Fluarix Tetra*) in participants aged 65 years and older in India.

Protocol version 2.0, dated 05 May 2023

I have read and understand the protocol and agree that it contains the ethical, legal, and scientific information necessary to participate in this trial. My signature confirms the agreement of both parties that the trial will be conducted in accordance with the protocol and all applicable laws and regulations including, but not limited to Good Clinical Practice (GCP), and the ethical principles that have their origins in the Declaration of Helsinki and applicable privacy laws.

I will provide copies of this protocol as needed to all physicians, nurses, and other professional personnel responsible to me who will participate in the Trial. I will discuss the protocol with them to assure myself that they are sufficiently informed regarding the conduct of the Trial. I am aware that this protocol will need to be approved by an appropriate reviewing Ethics Committee prior to any participants being enrolled and that I am responsible for verifying whether that requirement is met. I agree to adhere to the attached protocol and if requested to provide copies of medical information for the purpose of verification of submitted information, I will comply.

Since the information in this protocol is confidential, I understand that its disclosure to any third parties, other than those involved in approval, supervision, or conduct of the trial is prohibited. I will ensure that the necessary precautions are taken to protect such information from loss, inadvertent disclosure, or access by third parties.

Investigator:(Local investigator from the trial site, each site has one signature)

Name_____ _____

Signature Date

_____

Name of Institution

RETURN ORIGINAL TO IQVIA

Sponsor Signature Page

Reviewed and approved by:

Vishal Jain		Sr. Clinical Science Lead	
GSK	**Signature**	**Title**	**Date**
Pascal Peeters		Sr. Dir. Clinical Project Lead	
GSK	**Signature**	**Title**	**Date**

Informational Contacts

Sponsor

GSK Belgium is the Sponsor of the trial. It is the responsibility of the sponsor and its local affiliate in India (GSK India) who is the Marketing Authorization Holder (MAH) to ensure proper monitoring of the trial and compliance with all applicable regulatory guidelines and laws.

Sponsor Contact: **Pascal Peeters**

Sr. Dir. Clinical Project Lead

GlaxoSmithKline Biologicals SA
Rue de l'Institut 89, 1330 Rixensart, Belgium

Clinical Research Organization (CRO) responsible for the management of the trial

IQVIA, 3 Forbury Place, 23 Forbury Road, Reading, RG1 3JH, UK

List of Abbreviations

AE	Adverse event
CBER	Center for Biologics Evaluation and Research
CDC	Centers for Disease Control and Prevention
CI	Confidence interval
CONSORT	Consolidated Standards of Reporting Trials
CRF	Case report form
CRO	Contract research organization
DMP	Data management plan
DOH	Declaration of Helsinki
eCRF	Electronic case report form
EDC	Electronic data capture
EHR	Electronic Health Record
FDA	US Food and Drug Administration
GCP	Good Clinical Practice
GMT	Geometric mean titers
GPP	Good Pharmacoepidemiology Practice
HA	Hemagglutinin
HI	Hemagglutination inhibition
IB	Investigator brochure
I/M	Intramuscularly
IP	Investigational Process
ICF	Informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use

IEC	Independent ethics committee
IRB	Institutional review board
ISPE	International Society for Pharmacoepidemiology
MAE	Medically attended event
MedDRA	Medical Dictionary for Regulatory Activities
MGI	Mean geometric increase
NH	Northern Hemisphere
PT	Preferred term
QA	Quality assurance
SAE	Serious adverse event
SAP	Statistical analysis plan
SCR	Seroconversion rate
SoA	Schedule of Activities
SOC	System organ class
SPR	Seroprotection rate
TIVs	Trivalent influenza vaccines
WHO	World Health Organization
WHO DD	WHO Drug Dictionary

Study Synopsis

Full Study Title: A single-arm, open-label, multi-center, phase IV trial to evaluate the reactogenicity, safety, and immunogenicity of quadrivalent seasonal influenza vaccine (*Fluarix Tetra*) in participants aged 65 years and older in India.

Phase: Phase IV

Number of Participants: 250	**Duration of Participant Participation**: 22 Days

Background:

Influenza (flu) can cause mild to severe illness, ranging from mild fatigue to respiratory failure and death. Annual influenza vaccination is the most effective measure to reduce the risk of influenza infection and its complications. Globally, GlaxoSmithKline (GSK) Biologicals has been marketing an inactivated trivalent influenza split vaccine (Fluarix) since 1992. GSK received its first approval of Fluarix Tetra (a quadrivalent influenza split vaccine) on 14 December 2012 in the United States (US) for active immunization for the prevention of influenza disease caused by influenza virus types A and B contained in the vaccine at a dose of 0.5 mL. Fluarix Tetra is currently approved in the US, in 28 countries of European Economic Area (Germany as Reference Member State) as well as over 30 countries outside the European Union (EU) including United Kingdom (Great Britain) and India.

The present study is designed to evaluate the safety and immunogenicity of a *Fluarix Tetra* influenza vaccine (Northern Hemisphere [NH] 2023-2024) in adults aged 65 years of age and above in India.

Rationale: The National Centre for Disease Control (Ministry of Health and Family Welfare, Government of India) has recommended influenza vaccination for different groups considered to be at risk, across various age groups, including health care workers, pregnant women, persons with chronic illnesses, those who are immunocompromised and elderly individuals (≥65 years of age). GSK Vaccines' quadrivalent seasonal influenza vaccine D-QIV, *Fluarix Tetra,* has been approved for the immunization of adults and children ≥6 months of age in India. In order to fulfill a post-approval commitment imposed by the Indian regulatory agency, the present study is to generate additional evidence of safety and immunogenicity of 1 dose of *Fluarix Tetra* (NH 2023-2024), (0.5 mL) in participants aged 65 years and above in India.

Objectives and endpoints:

Primary Objective: To evaluate reactogenicity and safety of *Fluarix Tetra* single dose 0.5 mL intramuscularly (I/M) in participants aged 65 years and above in India.

Endpoints:

- Number and percentage of subjects with solicited adverse events (AEs) (local as well as general) for 7 days from the date of vaccination (Day 1).
- Number and percentage of subjects with unsolicited AEs starting from the date of vaccination for 21 days.
- Number and percentage of subjects with serious adverse events (SAEs) from the date of vaccination for 21 days.

Secondary Objective: To evaluate immunogenicity of *Fluarix Tetra* single dose 0.5 mL (I/M) in participants aged 65 years and above in India.

Endpoints:

- Geometric mean titers (GMT) of serum hemagglutination inhibition (HI) titers against the 4 influenza vaccine (or vaccine-like) strains at baseline (Day 1) and on Day 22.
- Mean geometric increase (MGI) at Day 22. MGI is defined as the fold increase in post-vaccination serum HI GMTs (Day 22) compared to Day 1.
- Seroconversion rate (SCR) at Day 22. SCR is defined as the percentage of subjects who have either a pre-vaccination titer < 1:10 and a post-vaccination titer ≥ 1:40 or a pre-vaccination titer ≥ 1:10 and at least a 4-fold increase in post-vaccination titer.
- Seroprotection rate (SPR) at Day 1 and Day 22. SPR is defined as the percentage of subjects with a serum HI titer ≥ 1:40.

Study design:

Overview of study design: A prospective, single-arm, open-label, multi-center, Phase IV trial.

Study sites: This trial will be conducted in multiple sites during NH influenza season in India.

Vaccination schedule: A single 0.5 mL intramuscular dose of *Fluarix Tetra* (NH 2023-2024), will be administered.

Safety and reactogenicity monitoring:

- Recording of solicited AEs for 7 days after vaccination
- Recording of unsolicited AEs for 21 days after *Fluarix Tetra* is administered
- Recording of SAEs for 21 days after vaccination

Immunogenicity assessment:

- **Blood Samples**: Two 5 mL blood samples will be collected, one before administration of a single dose of study vaccine at Day 1 and one at Day 22.
- **Laboratory testing**: Serum HI titers will be measured against the 4 influenza strains that the *Fluarix Tetra* are designed to protect against. GMT, MGI, SCR and SPR shall be evaluated to assess immunogenicity.

Type of study vaccine intervention: Open-label.

Data collection:

- Safety data - A diary card will be provided to study participants. Data will be collected from completed diary card daily by the participant and a telephone call follow-up by Investigator team will be performed to assess participant's health status. SAEs, if any, will be reported using the SAE Reporting Form.
- Sample collection data for Immunogenicity assessments- Blood samples will be collected on pre-vaccination at Day 1 and post-vaccination at Day 22. Samples will be tested using HI assay at GSK or GSK designated laboratory.

Data collection/ Data Sources:

A Diary card will be provided to trial participants to complete on a daily basis. The completed diary card will be collected from the participant on Day 22, and data will be captured in the electronic case report form (eCRF). The investigator team will follow-up via a telephone call between Day 8-10 to assess the participant's health status.

For safety assessment, vital signs and physical examination data on Day 1 will be assessed and recorded in the eCRF. Solicitated AEs up to Day 7 and unsolicited AEs and SAEs up to Day 21 will be recorded and transcribed into the eCRF.

Data Management and Quality Assurance:

A data management plan (DMP) will be created before data collection begins and will describe all functions, processes, and specifications for data collection, cleaning, and validation. The Investigator will maintain a record of the location(s) of their respective essential documents, including source documents. The storage system used during the trial and for archiving (irrespective of the type of media used) will provide document identification, version history, search, and retrieval. Representatives of the Sponsor's quality assurance (QA) unit/ monitoring team and competent regulatory authorities must be permitted to inspect all trial-related documents and other materials at the site, including the Investigator Site File, the completed eCRFs and the participants' original medical records. Audits may be conducted at any time during or after the study to ensure the validity and integrity of the study data.

Safety:

All the AEs, SAEs and other safety reporting data will be collected as per GSK standard procedures:

- Recording of solicited AEs for 7 days after vaccination
- Recording of unsolicited AEs for 21 days after vaccination
- Recording of SAEs for 21 days after vaccination
- AEs leading to discontinuation

Trial participants will be provided with a diary card at the time of vaccination to record the occurrence and intensity of solicited local and general AEs during the first 7 days after vaccination and of unsolicited AEs within 21 days after vaccination. These diary cards will be reviewed at the trial visit following the vaccination visit. All solicited local AEs will be considered to be causally related to vaccination. Causality of all other AEs will be assessed by the Investigator. Any AEs and SAEs reported after 21 days will be reported by the Investigator as per Indian regulatory requirement.

Statistical Considerations:

Sample size: Approximately 250 participants will be enrolled in this trial to achieve 200 evaluable participants considering 20% (N=50) of participants for possible drop-outs or invalid data.

With N=250, the width of the 95% CIs for the incidences correspond to the very common (≥1/10) AEs will always be <13%, and for uncommon and common AEs it will be ≤3%. The probability of observing at least 1 participant with an AE will be above 91% for common and very common AEs.

Interim and Final Analyses: There will be no interim analysis. The final analysis will be performed when all data, up to the end of the trial, are available and completely cleaned.

Ethical and Regulatory Considerations:

This Phase IV clinical trial will be conducted in accordance with the protocol and all applicable laws and regulations including, but not limited to Good Clinical Practice (GCP), Good Pharmacoepidemiology Practice (GPP), the ethical principles that have their origins in the Declaration of Helsinki (DOH) and applicable privacy laws. Data protection and privacy regulations will be strictly observed in capturing, forwarding, processing, and storing participant data. Every effort will be made to protect participant confidentiality according to the DOH, international ethical guidance and country regulatory requirements on the protection of individuals. An institutional review board (IRB)/ independent ethics committee (IEC) must review and approve the protocol and informed consent form (ICF) before any participants are enrolled. Before any protocol-directed data collection is performed, the participant must sign and date the IRB/ IEC-approved ICF.

Documentation of Protocol Amendments

Section Number Section Title Protocol page	Change made	Rationale
List of Abbreviations, p.11, p.12	Added the following abbreviations: Hemagglutinin (HA) Northern Hemisphere (NH) World Health Organization (WHO)	To maintain consistency in the study document
Study Synopsis, p.15, p.16 Section 5, Study Design, Section 5.1 , Study Description, Schedule of Activities, p.28, p.29, p.30, Section 5.3.4,	Abbreviation - DC was expanded to Diary card across the document	To maintain consistency in the study document

Section Number Section Title Protocol page	Change made	Rationale
Compliance with Study Treatment, p.36, Section 5.5.1, Time Period and Frequency for Collecting AE and SAE Information, p.40, Section 5.5.2, Method of Detecting AEs and SAEs, p.41, Section 5.7, Data Sources and Collection, p.49, p.50, Section 6.4.6, Limitations of Research Methods, p.57, Section 7.3, Source Documents, p.59		
Study Synopsis p.15, p.17 Section 5, Study Design, Section 5.1, Study Description p.28	Study design section Safety and reactogenicity monitoring Safety - Removed following brackets (Day 1 to Day 7) and (Day 1 to Day 21)	Removed additional information in the bracket for better clarity

Section Number Section Title Protocol page	Change made	Rationale
Section 1, Background, p.24	Recently, US Centers for Disease Control and Prevention (CDC) estimated 26 000 000 to 51 00 000 cases of seasonal influenza with the mortality of 19 000 to 56 000, from 01 October 2022, through 8 April 2023 (preliminary data).	Updated information from CDC for the year 2022-2023
Section 1, Background, p.25	This trial will use the updated formulation for the *Fluarix Tetra* (NH 2023-2024) as per the WHO recommendation [WHO 2023].	Added information as per WHO recommendations issued in February 2023 for use of updated formulation of the Fluarix *Tetra* vaccine (NH 2023-2024).
Section 2, Rationale, p.25	Added *Fluarix Tetra* (NH 2023-2024)	Updated as above
Section 5, Study Design, p.27, p.28	**Vaccination schedule**: A single 0.5 mL IM dose of *Fluarix Tetra* (NH 2023-2024) will be administered. Added information on the composition of the *Fluarix Tetra* (NH 2023-2024) vaccine **Laboratory testing**: Serum HI titers will be measured against the 4 influenza strains *Fluarix Tetra* (NH 2023-2024) is designed to protect against (vaccine or vaccine-like strains). GMT, SCR, MGI, and SPR will be evaluated to assess immunogenicity	Updated information on the formulation of Fluarix *Tetra* vaccine that will be used was added.
Section 4 Objectives p.27 and Section 5.4.1 Immunogenicity measures p.37	Secondary endpoint: Geometric mean titers (GMT) of serum hemagglutination inhibition (HI) titers against the 4 influenza vaccine strains at baseline (Day 1) and on Day 22. • Mean geometric increase (MGI) at Day 22. MGI is defined as the fold increase in post-vaccination serum HI GMTs (Day 22) compared to Day 1.	Day 21 has been changed to Day 22 to align with previous GSK studies/trials To align with language in the synopsis

Section Number Section Title Protocol page	Change made	Rationale
Section 5, Study Design, p.30	• Seroconversion rate (SCR) at Day 22. SCR is defined as the percentage of subjects who have either a pre-vaccination titer < 1:10 and a post-vaccination titer ≥ 1:40 or a pre-vaccination titer ≥ 1:10 and at least a 4-fold increase in post-vaccination titer. • Seroprotection rate (SPR) at Day 1 and Day 22. SPR is defined as the percentage of subjects with a serum HI titer ≥ 1:40. Figure 1. Study design, Visit schedule updated Updated to show that blood collection on Day 1 prior to vaccination. Updated to reflect the exact dates Day 8 +2 for contact and Day 22+3 for final blood draw.	To provide more clarity To align with previous GSK studies/trial
Section 5.2.1, Inclusion Criteria, p.31	Updated • Male or female participants aged ≥65 years of age • Participants and/or legally acceptable representative (s) (LAR) who in the opinion of the Investigator, can and will comply with the requirements of the protocol (e.g. completion of the diary cards, return for follow-up visits • Written or witnessed/thumb printed informed consent obtained from the participant and/or participant's LAR(s) after the study has been explained according to the local authority requirements and prior to performance of any study-specific procedure	To align with the approved indication of Fluarix Tetra, which does not have any reference to current Indian national CDC guideline for flu vaccination To align the language with standard text used in GSK studies/trials To align the language with standard text used in GSK studies/trials and to include the role of LAR. Also, to clarify that thumb printed informed consent is acceptable for illiterate trial subjects
Section 5.3.2, Preparation/ Handling/	Instructions for administration of the vaccine are presented in the Pharmacy Manual.	Updated as per the Pharmacy manual

Section Number Section Title Protocol page	Change made	Rationale
Storage/ Accountability of Study Treatment, p.35		
Section 5.4.3, Physical Examinations, p.38	A physical examination of each participant will be performed before vaccination. The collected information will be recorded in the medical history section of the eCRF.	Updated "medical history section of the" eCRF to provide more clarity in the data capture
Section 5.5, Adverse Events p.39	Pre-existing conditions or signs and/or symptoms present in a participant before the administration of the study vaccine.	Removed first dose from the sentence as only single dose will be administered.
Section 6.3, Populations for Analyses, Table 9. Analysis Set p.54	The Exposed Set will include all participants from the Enrolled Set who received the study vaccine. The Per Protocol Set will include all participants from the Enrolled Set who received the study intervention as per protocol,	Updated and removed "a single dose", Updated and removed "even single dose" As only single dose will be administered.
Section 8.1 Definitions, p.62	Detailed SAE definitions have been added	As per the GSK guidelines
Section 8.2, Procedures for Reporting Adverse Events in the CRF p.63	Each suspected AE occurring during the study must be recorded in the eCRF and/or specific AE forms as designated by the GSK, including the description, seriousness criteria, severity, duration onset and resolution date, causal relationship with the study treatment, actions taken with the study treatment (withdrawal), any other required treatment, and outcome.	Removed "dose reduction" as not applicable in the study
Section 9.4, Participant Confidentiality, p.66	However, race and ethnicity information will be collected as a part of demographics to determine the diversity in the clinical study participation.	Information on data collection for ethnic and racial background added with justification.

Section Number Section Title Protocol page	Change made	Rationale
Section 10, References, p.68	CDC, 2023. 2022-2023 U.S. Flu Season: Preliminary In-Season Burden Estimates. centers for disease control and prevention. Available at https://www.cdc.gov/flu/about/burden/preliminary-in-season-estimates.htm WHO 2023. Recommendations announced for influenza vaccine composition for the 2023-2024 northern hemisphere influenza season. Available at https://www.who.int/news/item/24-02-2023-recommendations-announced-for-influenza-vaccine-composition-for-the-2023-2024-northern-hemisphere-influenza-season	Added reference to CDC website with updated information for 2023. Added reference to recent WHO recommendations for use of influenza vaccine composition for the 2023-2024 NH influenza season.

1. BACKGROUND

Influenza is a common respiratory infection caused by influenza virus and transmitted through respiratory droplets [Wright, 2007]. Influenza occurs in seasonal epidemics and manifests as an acute febrile illness with variable degrees of systemic symptoms, ranging from mild fatigue to respiratory failure and death [Dangi, 2012].

Globally, it is estimated that 291 243 to 645 832 seasonal influenza-associated respiratory deaths (4.0 to 8.8 per 100 000 individuals) occur annually [Iuliano, 2018], 36% of which occur in low and middle-income countries like India [Narayan, 2020]. Recently, US (United States) Centers for Disease Control and Prevention (CDC) estimated 26 000 000 to 51 00 000 cases of seasonal influenza with the mortality of 19 000 to 56 000, from 01 October 2022, through 8 April 2023 (preliminary data). Mortality was the highest in infants and elderly persons [CDC, 2023]. An Indian study reported high burden of influenza-associated mortality among adults ≥65 years (51.1, (95% confidence interval (CI) = 9.2 - 93.0) deaths per 100 000 population). Influenza-associated cardiovascular death rates were also higher for the ≥65-year age group (71.8, 95% CI = 7.9 - 135.8 per 100 000) as compared to those aged <65 years (1.9, 95% CI = 0 - 4.6 per 100 000) [Narayan, 2020]. These estimates may inform strategies for influenza prevention and control in India, including the use of vaccines.

Annual influenza vaccination is the most effective measure to reduce the risk of influenza infection and its complications. Globally, GlaxoSmithKline (GSK) Biologicals has been marketing an inactivated trivalent influenza split vaccine (Fluarix) since 1992. Fluarix contains 15 mcg hemagglutinin (HA) of each of the recommended 3 inactivated split virion antigens. More than 434 million doses have been distributed worldwide, and the vaccine is registered in more than 100 countries. After the introduction of the quadrivalent inactivated split virion influenza vaccine (*Fluarix Tetra*), trivalent Fluarix license cancellation activities were initiated and are still ongoing in 2 international countries. *Fluarix Tetra* has been administered to millions of recipients without particular safety issues and has proven to be highly immunogenic. *Fluarix Tetra* is manufactured in the Dresden (Germany) plant by the same method as the commercial trivalent Fluarix vaccine except that it contains a second B-strain as a fourth inactivated split virion antigen. *Fluarix Tetra* was first approved on 14 December 2012 in the US for active immunization of adults and children 3 years and older for the prevention of disease caused by the influenza A subtype viruses and type B viruses contained in the vaccine. *Fluarix Tetra* is currently approved for active immunization of population from 6 months of age and older in the US, in 28 countries of European Economic Area (Germany as Reference Member State) as well as over 30 countries outside the European Union

(EU) including United Kingdom (Great Britain) and India. The brand name of *Fluarix Tetra* is Fluarix Quadrivalent in the US, *Fluarix Tetra* in the UK, *Fluarix Tetra* in France, Alpharix-Tetra in Belgium, and Influsplit Tetra in Germany.

The present trial is designed to evaluate the safety and immunogenicity of Fluarix *Tetra* influenza vaccine in adults aged 65 years of age and above in India. This trial will use the updated formulation for the *Fluarix Tetra* (Northern Hemisphere [NH] 2023-2024) as per the World Health Organization (WHO) recommendation [WHO 2023].

2. RATIONALE

Influenza causes substantial morbidity and mortality worldwide. In the Indian context, estimated influenza-associated mortality rates are the highest for those aged ≥65 years. These estimates may inform strategies for influenza prevention and control in India, such as possible vaccine introduction [Narayan, 2020]. The National Centre for Disease Control (Ministry of Health and Family Welfare, Government of India) has recommended influenza vaccination in the following categories of persons across various age groups such as health care workers, pregnant women, persons with chronic illnesses, those who are immunocompromised and elderly individuals (≥65 years of age). GSK Vaccines' quadrivalent seasonal influenza vaccine D-QIV, *Fluarix Tetra,* has been approved for the immunization of adults and children ≥6 months of age in India. GSK has committed to gather additional evidence of the safety and immunogenicity of 1 dose of *Fluarix Tetra* (0.5 mL) in individuals aged 65 years and above to fulfill a post-approval condition imposed by the Indian regulatory authorities (CDSCO) for this age group in India.

Clinical benefit of the vaccine has been demonstrated in a large, appropriately designed immunogenicity trial [Kieninger, 2013; US PI]. The most frequently reported local solicited adverse events (AEs) in participants aged 65 years and above were pain at injection site, fatigue, muscle ache and headache. Allergic reaction is a risk observed with multiple vaccines, including the influenza vaccines already licensed in the US. Therefore, the risk of allergic reaction to *Fluarix Tetra* has not affected the favorable benefit risk profile of *Fluarix Tetra* [Clinical Review, Fluarix Quadrivalent].

This study is designed to assess the frequency and severity of solicited AEs experienced within 7 days and unsolicited AEs experienced within 21 days post-vaccination with *Fluarix Tetra* (NH 2023-2024). Serious Adverse Events (SAEs) will also be recorded within 21 days post-vaccination.

3. BENEFIT/ RISK AND ETHICAL ASSESSMENT

The influenza virus is an important respiratory pathogen that causes annual epidemics and occasional pandemics. Virtually every year, epidemic influenza has a significant impact in terms of morbidity, mortality, and economic burden. Vaccination is presently the most effective way of controlling influenza and preventing its complications and mortality in persons at risk. Annual trivalent influenza vaccines (TIV) containing 2 A strains (H1N1 and H3N2) and 1 B-strain, which are intended to provide protection against influenza viruses that are expected to circulate in the upcoming season, have been used against seasonal influenza. However, since 1983, 2 antigenically and genetically distinct lineages of influenza B have co-circulated worldwide. As a consequence of the co-circulation of these 2 lineages, there is a certain degree of mismatch each season between the B-strain contained in the trivalent vaccine and the circulating B-strains. Since the 2 evolutionarily distinct lineages of influenza B virus continue to co-circulate, an additional B-strain antigen in the seasonal vaccine is expected to offer greater efficacy and broader protection. *Fluarix Tetra* is a quadrivalent influenza vaccine, comprising 2 A and 2 B-strains.

By participating in this study, the participant may benefit from being vaccinated with an inactivated quadrivalent influenza vaccine.

4. OBJECTIVES AND ENDPOINTS

Table 1. Study Objectives and Endpoints

Objective(s)	Endpoint(s)/Estimand(s)
Primary	
• To evaluate reactogenicity and safety of *Fluarix Tetra* single dose 0.5 mL intramuscularly (I/M) in participants aged 65 years and above in India.	• Number and percentage of subjects with solicited AEs (local as well as general) for 7 days from the date of vaccination (Day 1). • Number and percentage of subjects with unsolicited AEs starting from the date of vaccination for 21 days. • Number and percentage of subjects with SAEs from the date of vaccination for 21 days.
Secondary	

Objective(s)	Endpoint(s)/Estimand(s)
• To evaluate immunogenicity of *Fluarix Tetra* single dose 0.5 mL I/M in Participants aged 65 years and above in India.	• Geometric mean titers (GMT) of serum hemagglutination inhibition (HI) titers against the 4 influenza vaccine strains at baseline (Day 1) and on Day 22. • Mean geometric increase (MGI) at Day 22. MGI is defined as the fold increase in post-vaccination serum HI GMTs (Day 22) compared to Day 1. • Seroconversion rate (SCR) at Day 22. SCR is defined as the percentage of subjects who have either a pre-vaccination titer <1:10 and a post-vaccination titer ≥1:40 or a pre-vaccination titer ≥1:10 and at least a 4-fold increase in post-vaccination titer. • Seroprotection rate (SPR) at Day 1 and Day 22. SPR is defined as the percentage of subjects with a serum HI titer ≥1:40.

5. STUDY DESIGN

5.1 Study Description

Overview of study design: This trial is a prospective, multi-center, single-arm, open-label, Phase IV trial.

Study sites: This trial will be conducted in multiple sites during NH influenza season in India.

Study population: 250 participants aged 65 years and above in India will be enrolled.

Vaccination schedule: A single 0.5 mL I/M dose of *Fluarix Tetra* (NH 2023-2024) will be administered. The composition of the *Fluarix Tetra* (NH 2023-2024) vaccine is as follows:

A/Victoria/4897/2022 (H1N1) pdm09 - like strain* (A/Victoria/4897/2022, IVR-238)	15 micrograms HA**
A/Darwin/9/2021 (H3N2) - like strain* (A/Darwin/6/2021, IVR-227)	15 micrograms HA**
B/Austria/1359417/2021 – like strain* (B/Austria/1359417/2021, BVR-26)	15 micrograms HA**

B/Phuket/3073/2013 - like strain* (B/Phuket/3073/2013, wild type)	15 micrograms HA**

per 0.5 mL dose
* propagated in fertilized hens' eggs from healthy chicken flocks
** HA - hemagglutinin

Safety and reactogenicity monitoring through the daily diary card:

- Recording of solicited AEs for 7 days after vaccination
- Recording of unsolicited AEs for 21 days after vaccination
- Recording of SAEs for 21 days after vaccination

Immunogenicity assessment:

- **Blood Samples**: Two 5 mL blood samples will be collected, one before administration of a single dose of trial vaccine at Day 1 and one at Day 22
- **Laboratory testing**: Serum HI titers will be measured against the 4 influenza strains *Fluarix Tetra* (NH 2023-2024) is designed to protect against (vaccine or vaccine-like strains). Geometric mean titers (GMT), seroconversion rate (SCR), MGI, and SPR will be evaluated to assess immunogenicity.

Duration of the trial: 22 days per participant.

Type of study vaccine intervention: Open-label.

Data collection:

Safety data - Trial participants will receive a diary card. The Investigator team will follow-up via a telephone call on Day 8 to assess participant's health status. The completed diary card will be collected on Day 22. The Investigator team will capture the data in an electronic case report form (eCRF). SAEs will be reported using the SAE Reporting Form.

Sample collection for immunogenicity data - Blood samples will be collected pre-vaccination at Day 1 and post-vaccination at Day 22. Samples will be tested at GSK or GSK designated laboratory.

SCHEDULE OF ACTIVITIES (SoA)

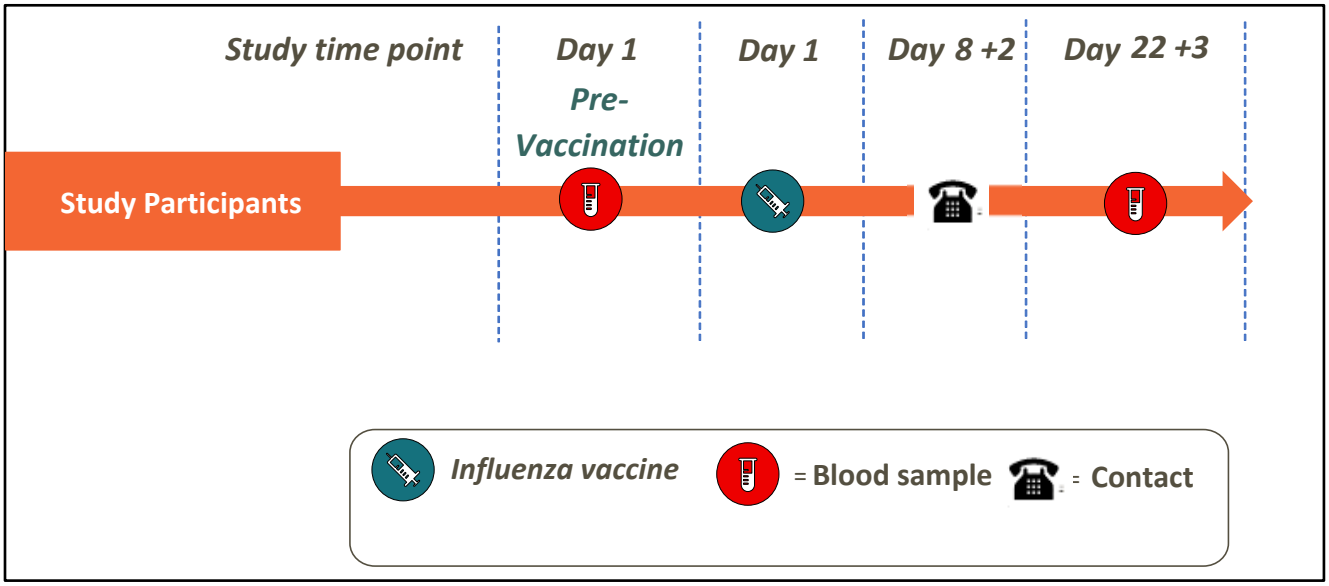
Table 2. Schedule of Activities

Data capture	Baseline	Follow-up (Telephonic)	End of trial
Time points	**Day 1**	**Day 8 (+2)**	**Day 22 (+3)**
Trial clinic visit	**1**		**2**
Informed consent	✓		
Inclusion and exclusion criteria	✓		
Enrollment	✓		
Questionnaire survey	✓		
Physical exam and vital signs	✓		
Blood sample collection for serum immunogenicity assessments[a]	✓		✓
Administration of *Fluarix Tetra* vaccine	✓		
Provide diary card for reporting daily health status	✓		
Phone contact for safety follow-up and diary card assessment[b]		✓	
Recording solicited AEs[c]	✓	✓	
Recording unsolicited AEs, SAEs[d] and AEs leading to withdrawal from the study	✓	✓	✓
Return of paper diary card *(Review for completeness of diary cards)*			✓
Trial conclusion			✓

AE: adverse event; SAE: serious adverse event.

a) Sample to be collected pre-vaccination at Day 1 and post-vaccination at Day 22 (+3)
b) The telephonic follow-up with participant will be conducted on Day 8 (+2).
c) Recording solicited AEs on a daily basis for 7 days
d) Recording unsolicited AEs and SAEs for 21 days

Figure 1. Schematic Design, Visit schedule



5.1.1 Scientific Rationale for the Study Design

The prospective, multi-center, single-arm, open-label, Phase IV trial can accomplish the study objectives:

- To evaluate the safety and reactogenicity of *Fluarix Tetra*
- To evaluate the humoral immunogenicity in terms of GMTs, MGI, SCR, and SPR with respect to the viral strains included in *Fluarix Tetra*

5.1.2 Justification of the Dose

As per [Kieninger, 2013]; US PI, post-vaccination, 0.5 mL dose of *Fluarix Tetra* achieved the lower geometric mean antibody titers GMTs and SCR among ≥65 years of age vaccinees compared to younger participants (aged 18 through 64 years). The HI antibody responses against all 4 strains fulfilled the Center for Biologics Evaluation and Research (CBER) immunogenicity acceptance criteria in trial participants ≥65 years of age. The reactogenicity and safety profiles of

Fluarix Tetra were comparable in this age group (≥65 years) to that in a younger population. Thus, a single dose of 0.5 mL IM will be used in this trial.

5.1.3 End of Study Definition

The end of the trial is defined as the date of the last visit of the last participant in the trial or last scheduled procedure shown in the Schedule of Activities (SoA) for the last participant in the trial. A participant is considered to have completed the trial if he/she has completed all scheduled visits of the trial and data are available for protocol analysis.

5.2 Study Population

The trial will aim to enroll approximately 250 participants from multiple centers in India.

5.2.1 Inclusion Criteria

Deviations from inclusion criteria are not allowed because they can potentially jeopardize the scientific integrity of the trial. Therefore, adherence to the criteria as specified in the protocol is essential.

The following criteria must be met in order to be enrolled in the trial:

- Male or female participants aged ≥65 years of age.
- Participants and/or legally acceptable representative(s) (LAR) who in the opinion of the Investigator, can and will comply with the requirements of the protocol (e.g. completion of the diary cards, return for follow-up visits).
- Written or witnessed/thumb printed informed consent obtained from the participant and/or participant's LAR(s) after the study has been explained according to the local authority requirements and prior to performance of any study-specific procedure.

5.2.2 Exclusion Criteria

Deviations from the exclusion criteria are not allowed because they can potentially jeopardize the scientific integrity of the trial. Therefore, adherence to the criteria as specified in the protocol is essential.

Participants meeting ANY of the following criteria are not eligible for participation:

- History of severe allergic reactions (e.g., anaphylaxis) to any component of the vaccine, including egg protein, or following a previous dose of any influenza vaccine.
- Receipt of licensed vaccine, immune sera and/or any blood products, or an investigational trial agent within previous 30 days or planned during their participation in the trial.
- Receipt of any flu vaccine within 6 months before trial start or any other vaccine within 30 days before the trial.
- Receipt of any dose of a COVID-19 vaccine within 15 days of trial start.
- History of Guillain-Barré Syndrome.
- Altered immune status or chronic administration (defined as more than 14 days) of immunosuppressants or other immune-modifying agents within 6 months prior to administration of trial vaccine.
- History of acute infectious disease or acute respiratory illness needing antibiotics or antivirals in the previous 7 days, based on Investigator's judgment.
- If a participant candidate has fever, the trial vaccination should be postponed to when the fever has resolved for at least 2 days (temporary exclusion criterion). Fever is defined as temperature ≥38.0°C (100.4°F) by any route. The preferred location for measuring temperature will be oral route.
- Acute or chronic clinically significant pulmonary, cardiovascular, hepatic, or renal functional abnormality, as determined by medical history, physical examination, or laboratory screening tests.
- Any other clinical condition that, in the opinion of the Investigator, might pose additional risk to the participant due to participation in the trial.

5.2.3 Study Enrollment

All participants presenting during the enrolment period will be assessed for eligibility according to the defined selection criteria and all eligible participants will be consecutively proposed to be enrolled in the trial. A screening log will be maintained by each site to record the disposition of consecutive participants potentially eligible for trial participation, in order to better assess the representativeness of the sampled population.

5.2.3.1 Screen Failures

Screen failures are defined as participants who consent to participate in the trial but are not subsequently enrolled in the trial. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any AE/SAE prior to vaccine administration.

5.2.3.2 Procedures for Handling Incorrectly Enrolled or Randomized Participants

Before data are locked for statistical analysis, a review of all data will occur. Any decision to exclude either a participant or single assessment from the statistical analysis will be justified and documented. Normally no data should be excluded from the exposed set. The participants or observations to be excluded and the reasons for their exclusion will be documented and signed by those responsible before the database lock. The participants and observations excluded from analysis sets, and the reason for this, will be described in the trial report.

5.2.4 Lifestyle Considerations

Not applicable

5.2.5 Participant Withdrawal and Discontinuation of Study Treatment

All data collected until the date of withdrawal of the participant will be used for the analysis.

Information related to the withdrawal of the participant will be documented. The Investigator will document whether the decision to withdraw a participant from the trial was made by the participant himself/herself, or by the Investigator, as well as which of the following possible reasons was responsible for the withdrawal:

- Protocol deviation, especially for inclusion/exclusion criteria
- SAE
- Solicited AE
- Unsolicited non-serious AE

- Consent withdrawal, not due to an AE
- Investigator discretion to discontinue the participants with appropriate reason
- Migrated/moved from the trial center
- Lost to follow-up
- Sponsor trial termination
- Other (please specify)

Participants who are withdrawn from the trial because of SAEs must be clearly distinguished from participants who are withdrawn for other reasons.

Withdrawn participants will not be replaced.

Discontinuation of Study Treatment: Not applicable.

Lost to Follow-up:

A Participant will be considered lost to follow-up if he or she fails to attend 2nd scheduled visit (Day 22) within the window of 3 days and is unable to be contacted by the trial center.

The following actions must be taken if a participant fails to return to the clinic for a required trial visit:

- The trial center must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant wishes to and/or should continue in the trial.
- Before a participant is deemed lost to follow-up, the Investigator or designee must make every effort to regain contact with the participant. These contact attempts should be documented in the participant's medical record.

5.3 Exposure Definition and Measures

The exposure under trial is administration of *Fluarix Tetra* vaccine. As this is a single-arm trial with no comparison group, there will be no exposure variable per se in the analyses of the primary and secondary endpoints. The associations between the exposure and the clinical parameters

investigated in the trial will be evaluated at baseline and at the end of the follow-up for the same participant.

5.3.1 Provision of Study Treatment

The Sponsor shall supply adequate doses of *Fluarix Tetra* to the Investigator site. The received vaccine doses will be verified for the sealed condition of packs and adequacy of label such as Project Number, Product Name, Strength, Number of Dosage, Manufacturer, Lot Number or Batch Number, Expiry Date and Storage Condition mentioned clearly (store at 2°C to 8°C) and with statement as 'Clinical Trial Use Only'.

The Investigator site pharmacy custodian or his/her designated trial personnel will receive the vaccine doses.

5.3.2 Preparation/ Handling/ Storage/ Accountability of Study Treatment

The Investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all trial treatment received and that any discrepancies are reported and resolved before use of the trial treatment. Only participants enrolled in the trial may receive trial treatment, and only authorized trial center staff may supply or administer trial treatment. All trial treatments must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the Investigator and authorized trial center staff.

Handling:

- The vaccine should be allowed to reach room temperature before use.
- Shake well before use. Inspect visually prior to administration.
- Instructions for administration of the vaccine are presented in the Pharmacy Manual.

Storage:

- Store in a refrigerator (2°C to 8°C).
- Do not freeze.
- Store in the original package in order to protect from light.
- Keep out of reach of children.

Accountability:

The Investigator, institution, or the head of the medical institution (where applicable) is responsible for trial treatment accountability, reconciliation, and record maintenance (i.e., receipt, reconciliation, and final disposition records). The Investigator, a member of the trial center staff, or a hospital pharmacist must maintain an adequate record of the receipt and distribution of all trial medication using the Drug Accountability Form. These forms must be available for inspection at any time. Further guidance and information for the final disposition of unused trial treatment are provided in the Pharmacy Manual.

5.3.3 Measures to Minimize Bias: Randomization and Blinding

Since this trial is single arm, randomization and blinding do not apply.

5.3.4 Compliance with Study Treatment

Compliance with trial treatment will be assessed among a number of participants for receiving flu vaccination at Day 1, missing visits and returning diary card.

5.3.5 Concomitant Therapy

Any medication (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements) that the participant is receiving at the time of enrollment (within 2 days before the time of enrollment) or receives during the trial must be recorded on the eCRF along with:

- Reason for use.
- Dates of administration, including start and end dates.
- Dosage information, including dose and frequency.

The Medical Monitor should be contacted if there are any questions regarding concomitant or prior therapy.

Rescue Medication

As with all injectable vaccines, appropriate medical treatment and supervision should always be readily available in case of an anaphylactic event following the administration of the vaccine. It is good clinical practice to precede vaccination by a review of the medical history (especially with regards to previous vaccination and possible occurrence of undesirable events) and a clinical

examination. The Investigator will manage untoward events of vaccine administration as per their clinical judgment.

5.3.6 Dose Modification

Not applicable.

5.3.7 Treatment After the End of the Study

The Sponsor will not provide any additional care to participants after they complete the trial.

5.4 Outcome Definitions and Measures

5.4.1 Immunogenicity Measures

- GMT of serum HI titers against the 4 influenza vaccine (or vaccine-like) strains at baseline (Day 1) and on Day 22.
- MGI, defined as the fold increase, in post-vaccination serum HI GMTs (Day 22) compared to Day 1.
- SCR, defined as the percentage of participants who have either a pre-vaccination titer <1:10 and a post-vaccination titer ≥1:40 or a pre-vaccination titer ≥1:10 and at least a 4-fold increase in post-vaccination titer.
- SPR, defined as the percentage of participants with a serum HI titer ≥1:40.

Biological samples will be used for research planned in the protocol and for purposes related to the improvement, development and quality assurance (QA) of the laboratory tests described in this protocol. Additional exploratory testing to characterize the immune response of the vaccine/vaccine components or to characterize the disease may be performed on the serum samples if deemed necessary for accurate interpretation of the data and/or should such test(s) become available in the GSK Biologicals' laboratory, or a laboratory designated by GSK Biologicals. These additional assays may not be represented in the objectives/endpoints of the study protocol. Serum might also be used for assay development/validation purpose outside of this protocol.

By default, collected samples will be stored for a maximum of 20 years. This storage period begins when the last participant performs the last study visit. This timeline can be adapted

based on local laws, regulations or guidelines requiring different timeframes or procedures. In all cases, the storage period should be aligned with participant's consent. These additional requirements must be formally communicated to, discussed and agreed with GSK

Please refer to the Laboratory Manual for details on biospecimen management (handling, storage and shipment). Tests will be conducted at the Sponsor's laboratory, or laboratories designated by the Sponsor.

5.4.2 Safety Measures

All the AEs, SAEs and other safety reporting will be captured as per GSK standard procedures.

- Solicited local symptoms during the 7-day post-vaccination follow-up
- Solicited general symptoms during the 7-day post-vaccination follow-up
- Unsolicited symptoms during the 21-day post-vaccination follow-up period
- SAEs during the 21-day post-vaccination follow-up period

5.4.3 Physical Examinations

A physical examination of each participant will be performed before vaccination. The collected information will be recorded in the medical history section of the eCRF. Treatment of any abnormality observed during the physical examination will be performed outside this trial according to local medical practice guidelines or by referral to an appropriate health care provider.

5.4.4 Vital Signs

Vital signs (blood pressure, pulse rate, respiratory rate, and body temperature) will be assessed pre-vaccination at Day 1.

5.4.5 Electrocardiograms

Not applicable.

5.4.6 Clinical Safety Laboratory Assessments

Not applicable.

5.4.7 Suicidal Risk Monitoring

Not applicable.

5.5 Adverse Events

Definition of AE: An AE is any untoward medical occurrence (an unfavorable/unintended sign - including an abnormal laboratory finding), symptom, or disease (new or exacerbated) in a trial participant that is temporally associated with the administration of a marketed vaccine. The AE may or may not be considered related to the marketed vaccine.

Events Meeting the AE Definition:

- Significant or unexpected worsening or exacerbation of the condition/indication under trial.
- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.
- New conditions detected or diagnosed following the performance of the administration of marketed vaccine even though they may have been present before trial start.
- Signs, symptoms, or the clinical sequelae of a suspected drug, disease, or other interaction.
- Signs, symptoms, or the clinical sequelae of administration error of either the marketed vaccine or a concurrent medication.
- Signs or symptoms temporally associated with the marketed vaccine.
- Signs, symptoms that require medical attention (e.g., hospital stays, physician visits and emergency room visits).
- Significant failure of an expected pharmacologic or biological action.
- Clinically significant abnormal laboratory findings or other abnormal assessments that are present at baseline and significantly worsen following the start of the trial will also be reported as AEs or SAEs.
- The signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfill the definition of an AE or SAE.

Events NOT Meeting the AE Definition

- Situations where an untoward medical occurrence did not occur (e.g., social and/or convenience admission to a hospital, admission for routine examination).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the trial that do not worsen.

- Pre-existing conditions or signs and/or symptoms present in a participant before the administration of the trial vaccine. These events will be recorded in the medical history section of the eCRF.
- Hospitalization for elective treatment of a pre-existing condition (known or diagnosed before signing the informed consent) that did not worsen from baseline.
- Any clinically significant abnormal laboratory findings or other abnormal safety assessments associated with the underlying disease, unless judged by the Investigator to be more severe than expected for the participant's condition.

Definition of SAE: A SAE is any untoward medical occurrence that:

a. Results in death.

b. Is life-threatening.

c. Requires hospitalization or prolongation of existing hospitalization.

d. Results in disability/incapacity.

e. Is a congenital anomaly/birth defect in the offspring of a trial participant.

Other adverse events (AEs): Other AEs not included in the list of solicitated AEs that are experienced by the participants within 21 days post-vaccination (i.e., the day of vaccination and the following 6 days) will be collected in the free-text field of the diary card. Other AEs include both serious and non-serious AEs.
Participants will be instructed to contact the Investigator immediately should they/the participant manifest any signs or symptoms perceived as serious/of concern or indicating a change in their health status.

5.5.1 Time Period and Frequency for Collecting AE and SAE Information

All solicited AEs that occur within 7 days and unsolicited AEs for 21 days following the administration of *Fluarix Tetra* must be recorded into the appropriate section of the eCRF, irrespective of intensity, as reported by the participant in the completed diary card.

All SAEs regardless of possible relation to vaccination should be reported in an expedited way throughout the study.

The Investigator or designee will record and immediately report to the Sponsor or designee all SAEs in enrolled participants occurring within 21 days post-vaccination via the eCRF. Reporting should, under no circumstances, occur later than 24 hours after the Investigator becomes aware of

the SAE. The Investigator will submit any updated SAE data to the Sponsor within 24 hours of it being available.

Medical occurrences that begin before the start of receipt of trial vaccine but after obtaining informed consent will be recorded on the Medical History/ Current Medical Conditions section of the eCRF, not the AE section.

Investigators are not obligated to actively seek AE or SAE after conclusion of the trial participation. However, if the Investigator learns of any SAE, including a death, at any time after a participant has been discharged from the trial, and he/she considers the event to be reasonably related to the trial treatment or trial participation, the Investigator must promptly notify the Sponsor.

5.5.2 Method of Detecting AEs and SAEs

A diary card will be used in this trial to capture solicited and other AEs. In addition to the participant completing and returning the diary card, the Investigator will record any occurrence of SAEs into the participant's eCRF to minimize potential missing data (e.g., when a participant's hospitalization prevents the completion of the diary). An AE that is assessed as severe should not be confused with a SAE. Severity is a categorization used for rating the intensity of an event; and both AEs and SAEs can be assessed as severe. An event is defined as 'serious' when it meets 1 of the pre-defined outcomes as described above (Section 5.5).

Assessment of Intensity

The intensity of the following solicited AEs will be assessed as described:

Table 3. Intensity Scales for Solicited Events in Adults 18 years of Age or More

Event	Intensity Grade	Parameter
Pain at administration-site	0	None
	1	Mild: Any pain neither interfering with nor preventing normal everyday activities
	2	Moderate: Painful when limb is moved and interferes with everyday activities
	3	Severe: Significant pain at rest. Prevents normal everyday activities
Headache	0	Normal
	1	Mild: Headache that is easily tolerated

Event	Intensity Grade	Parameter
	2	Moderate: Headache that interferes with normal activity
	3	Severe: Headache that prevents normal activity
Fatigue	0	Normal
	1	Mild: Fatigue that is easily tolerated
	2	Moderate: Fatigue that interferes with normal activity
	3	Severe: Fatigue that prevents normal activity
Muscle ache all over body	0	Normal
	1	Mild: Muscle aches that are easily tolerated
	2	Moderate: Muscle aches that interfere with normal activity
	3	Severe: Muscle aches that prevent normal activity
Joint pain	0	Normal
	1	Mild: Joint pain that is easily tolerated
	2	Moderate: Joint pain that interferes with normal activity
	3	Severe: Joint pain that prevents normal activity
Shivering (chills)	0	Normal
	1	Mild: Shivering (chills) that is easily tolerated
	2	Moderate: Shivering (chills) that interferes with normal activity
	3	Severe: Shivering (chills) that prevents normal activity
Sweating	0	Normal
	1	Mild: Sweating that is easily tolerated
	2	Moderate: Sweating that interferes with normal activity
	3	Severe: Sweating that prevents normal activity
Gastrointestinal symptoms: nausea, vomiting, diarrhea and/or abdominal pain	0	Normal
	1	Mild: Gastrointestinal symptoms that are easily tolerated
	2	Moderate: Gastrointestinal symptoms that interfere with normal activity
	3	Severe: Gastrointestinal symptoms that prevent normal activity
Redness at administration-site	Record greatest surface diameter in mm	
Swelling at administration-site	Record greatest surface diameter in mm	
Temperature*	Record temperature in °C/°F	

* Fever is defined as temperature ≥38.0°C (100.4°F) by any route. The preferred location for measuring temperature will be the oral route.

The maximum intensity of local injection site redness/swelling will be scored at GSK as follows:

0: ≤20 mm

1: >20 to 50 mm

2: >50 to 100 mm

3: >100 mm

The maximum intensity of fever will be scored at GSK as follows:

0: <38.0°C (<100.4°F)

1: ≥38.0–38.4°C (≥100.4–101.2°F)

2: ≥38.5–38.9°C (≥101.3–102.1°F)

3: ≥39.0–40.0°C (≥102.2–104.0°F)

4: >40.0°C (>104.0°F)

The Investigator will assess the maximum intensity that occurred over the duration of the event for all unsolicited AEs (including SAEs) recorded during the study. The assessment will be based on the Investigator's clinical judgment.

The intensity should be assigned to one of the following categories:

1 (mild)	=	An AE which is easily tolerated by the participant, causing minimal discomfort, and not interfering with everyday activities.
2 (moderate)	=	An AE which is sufficiently discomforting to interfere with normal everyday activities.
3 (severe)	=	An AE which prevents normal, everyday activities In adults, such an AE would, for example, prevent attendance at work/school and would necessitate the administration of corrective therapy.

An AE that is assessed as Grade 3 (severe) should not be confused with an SAE. Grade 3 is a category used for rating the intensity of an event; and both AEs and SAEs can be assessed as Grade 3. An event is defined as 'serious' when it meets 1 of the pre-defined outcomes as described in the Section 5.5.

Assessment of causality

All solicited administration-site and systemic events will be considered causally related to vaccination. The complete list of these events is provided in the Table 5.

The Investigator must assess the relationship between study vaccine/product and the occurrence of each unsolicited AE/SAE using clinical judgment. Where several different vaccines/products were administered, the Investigator should specify, when possible, if the unsolicited AE/SAE could be causally related to a specific vaccine/product (i.e., investigational, control/placebo or co-administered vaccine). When causal relationship to a specific vaccine/product cannot be determined, the Investigator should indicate the unsolicited AE/SAE to be related to all products.

Alternative plausible causes, such as natural history of the underlying diseases, concomitant therapy, other risk factors, and the temporal relationship of the event to the study vaccine/product will be considered and investigated. The investigator will also consult the investigator brochure (IB) to determine his/her assessment.

Causality should be assessed by the Investigator using the following question:

Is there a reasonable possibility that the unsolicited AE may have been caused by the study vaccine/product?

YES	:	There is a reasonable possibility that the study vaccine/product contributed to the AE.
NO	:	There is no reasonable possibility that the AE is causally related to the administration of the study vaccine/product. There are other, more likely causes and administration of the study vaccine/product is not suspected to have contributed to the AE.

If an event meets the criteria to be determined as 'serious' (see Section 5.5), additional examinations/tests will be performed by the Investigator to determine ALL possible contributing factors for each SAE.

Possible contributing factors include:

- Medical history.
- Other medication.

- Protocol required procedure.
- Other procedure not required by the protocol.
- Lack of efficacy of the vaccine/product, if applicable.
- Erroneous administration.
- Other causes: There may be situations when an SAE has occurred, and the Investigator has minimal information to include in the initial report to GSK. However, it is very important to record an assessment of causality for every event.

The causality assessment is one of the criteria used when determining regulatory reporting requirements. The Investigator may change his/her opinion of causality after receiving additional information and update the SAE information accordingly.

(1) Medically attended visits

For each solicited and unsolicited symptom the participant experiences, the participant will be asked if he/she received medical attention defined as hospitalization, or an otherwise unscheduled visit to or from medical personnel for any reason, including emergency room visits. This information will be recorded in the eCRF.

(2) Assessment of outcomes

The Investigator will assess the outcome of all unsolicited AEs (including SAEs) recorded during the study as:

- Recovered/resolved.
- Recovering/resolving.
- Not recovered/not resolved.
- Recovered with sequelae/resolved with sequelae.
- Fatal (SAEs only).

5.5.3 Follow-up of AEs and SAEs

After the initial AE/SAE report, the Investigator will proactively follow each participant at subsequent visits/contacts. All SAEs will be followed until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up, or until the trial is concluded.

5.5.4 Regulatory Reporting Requirements for SAEs

It will be clearly communicated to participating investigators that the trial does not replace the reporting of AEs/SAEs that should occur as part of routine practice as specified by local regulations. It is not the intention of the trial to influence or change the usual local reporting processes. Investigators should continue to report any AEs/SAEs they would typically report using the mechanisms routinely used in their healthcare practice. Therefore, although the data collected for this trial are primarily safety-related data, reporting mechanisms of AEs to regulatory authorities should not be altered and are to continue according to local standards.

If an investigator (or designee) becomes aware that a trial participant has experienced a SAE within 21 days post-vaccination, it must be reported to Sponsor using the eCRF and within the timeframes mentioned in below Table 4. This is essential for meeting Sponsor legal obligations and ethical responsibilities for participant safety and the safety of a marketed vaccine. The report must be completed as thoroughly as possible, with all available details of the event. The SAE will be linked to the central safety database with a trial ID link mechanism and reporting to Indian regulatory authority will be performed as per their requirement.

For SAEs related to the marketed vaccine, the investigator must always provide an assessment of causality at the time of the initial report.

The Sponsor will comply with country-specific regulatory requirements related to safety reporting to the regulatory authority, institutional review board/independent ethics committee (IRB/IEC), and investigators.

Table 4. Timeframes For Submitting SAEs

Type of Event	Initial Reports		Follow-up of Relevant Information on a Previous Report	
	Timeframe	Documents	Timeframe	Documents
SAEs	24 hours	eCRF	14 Calendar days	eCRF, SAE Form, Table 5 as per NDCT Rule 2019 and relevant medical records

eCRF: electronic Case Report Form; SAE: serious adverse event, NDCT: New Drug and Clinical Trials

Backup System in Case the Electronic Reporting System Does Not Work

If the electronic reporting system does not work, the Investigator (or designee) must report the SAE directly to Sponsor central safety within the required timeframe.

Contact information for reporting SAEs to Sponsor in case the electronic reporting system does not work

Study contact for reporting SAEs in case the eCRF reporting system does not work
24/24 hour and 7/7 day availability: GSK Clinical Safety & Pharmacovigilance Fax: +32 2 656 51 16 or +32 2 656 80 09 Email address: PV.ICSRManagement@gsk.com

5.5.5 Pregnancy

Not applicable.

5.5.6 Solicited Adverse Events

AEs that comprise the primary interest of the study are designated as solicited AEs. The list of pre-specified solicited AEs is listed below:

Table 5. List of Pre-Specified Solicited AEs

Solicited Administration-site Events
Pain
Redness
Swelling
Solicited Systemic Events
Fever
Headache
Myalgia (Muscle pain)
Arthralgia (Joint pain)
Fatigue
Gastrointestinal symptoms (including nausea, vomiting, diarrhea and/or abdominal pain)
Sweating
Shivering

Body temperature will be recorded preferably in the evening and in case temperature was measured more than once per day, the highest temperature will be recorded in the eCRF.

5.5.7 Disease-related Events and/or Disease-related Outcomes Not Qualifying as Adverse Events or Serious Adverse Events

Not applicable.

5.6 Treatment of Overdose

Not applicable.

5.6.1 Other Measures (If Applicable)

Not applicable.

5.7 Data Sources and Collection

A diary card will be provided to trial participants to fill it on a daily basis. The completed diary card will be collected from the participant on Day-22 and data will be captured in the eCRF. A telephone follow-up call will be performed by the Investigator team to assess the participant's health status.

Blood sample collection for immunogenicity data will be collected pre-vaccination at Day 1 and post-vaccination at Day 22. The Investigator team will capture the data in an eCRF. SAEs, if any, will be reported using the SAE Reporting Form.

For safety assessment, vital signs and physical examination data at Day 1 will be assessed and recorded in the eCRF. Solicited AEs up to Day 7, unsolicited AEs up to Day 21 and SAEs up to Day 21 will be recorded in the paper diary card by participant and transcribed into the eCRF.

Table 6. Data Collection Schedule

Visit number	**Baseline**	**Follow-up (Telephonic)**	**End of Study**
Time points	**Day 1**	**Day 8 (+2)**	**Day 22 (+3)**
Informed consent	✓		
Inclusion and exclusion criteria	✓		
Physical examination	✓		
Demographic data	✓		
Medical history	✓		
History of Flu vaccination	✓		
Current medical condition	✓	✓	✓
Concomitant medication	✓	✓	✓
Vital signs	✓		
Data related to sample collection	✓		✓
Telephonic data collection		✓	

Visit number	Baseline	Follow-up (Telephonic)	End of Study
Time points	**Day 1**	**Day 8 (+2)**	**Day 22 (+3)**
Diary card data collection			✓
Trial conclusion			✓

5.7.1 Baseline/ Enrollment

The following data will be collected at baseline for all enrolled participants:

- Demographics (age, year of birth, ethnicity, race, and sex)
- Medical history
- History of flu vaccination for last 3 years
- Current medical condition
- Vitals
- Physical examination
- Immunogenicity assessment parameters: GMT, MGI, SCR and SPR

5.7.2 Follow-up

The following data will be collected for all enrolled participants at the telephonic follow-up timepoint:

- Current medical condition
- Any AEs
- Assessment of patient diary card

The following data will be collected in eCRF for all enrolled participants at Day 22 which is end of trial for the participant:

- Current medical condition

- Immunogenicity assessment parameters: GMT, MGI, SCR and SPR
- SAEs
- Solicited and unsolicited AEs
- Study conclusion data

5.7.3 Participant Discontinuation/Withdrawal

Refer to section 5.2.5.

6. STATISTICAL METHODS

6.1 Statistical Hypotheses

All analyses will be descriptive. No hypothesis will be tested.

6.2 Sample Size

Approximately 250 participants will be enrolled in this trial to achieve 200 evaluable participants considering that some participants may drop out of the study or some may not be included in data analysis due to missing or invalid data.

Table 7. 95% Clopper-Pearson (exact) Confidence Intervals and Probabilities to Observe at least One Participant with AE for N=250 Participants, with Varying Percentages of Participants with AEs.

		95% CI[1]			
	Category	Lower Limit	Upper Limit	Width	Probability to Observe ≥1 Participant with AE (%)[2]
0.1%	Uncommon	0.00	1.67	1.67	22.1
1%	Common	0.17	3.17	3.00	91.9
10%	Very common	6.58	14.41	7.83	>99.9
50%		43.63	56.37	12.73	>99.9

1. Calculations done using SAS version 9.4 and validated using PASS (19) software.
2. Calculated using the binomial distribution.

Table 7 shows 95% Clopper-Pearson CIs for the proposed N=250 and varying incidence of solicited/ unsolicited AEs. The AE incidences shown correspond to the categories uncommon (≥1/1 000 to <1/100), common (≥1/100 to <1/10) and very common (≥1/10).

With N=250, the width observed for the 95% CIs is always <13%, and for uncommon and common AEs it is ≤3%.

Table 7 also shows, in the last column, the probability of observing at least 1 participant with AE. This probability is at least 91.9% for common and very common AEs.

Table 8. 95% Clopper-Pearson Exact Confidence Intervals and Probabilities to Observe at least One Participant with SAE for N=250 Participants, with Cumulative Incidence up to 1% Over a 6-month Period.

		Clopper-Pearson 95% CI[1]			
Months after Vaccination	Cumulative Incidence of SAE (%)[2]	Lower Limit (%)	Upper Limit (%)	Width	Probability to Observe ≥1 participant with SAE (%)[3]
1	0.17	0.00	1.79	1.79	34.1
2	0.33	0.00	2.09	2.09	56.6
3	0.50	0.02	2.38	2.35	71.4
4	0.67	0.06	2.65	2.59	81.2
5	0.83	0.11	2.91	2.80	87.7
6	1.00	0.17	3.17	3.00	91.9

1. SAS version 9.4 and validated using PASS (19) software.
2. Assuming linear increase in incidence from date of vaccination to 1% at 6 months.
3. Calculated using binomial distribution.

Table 8 shows 95% Clopper-Pearson CIs for 250 participants by cumulative incidence of SAE. The width of the 95% CIs is ≤ 3% throughout. The probability of observing at least 1 participant with SAE is >56% for cumulative incidence from Month 2 onward [Clopper_1934].

Further details about the actual implementation of the Clopper-Pearson CIs will be provided in the Statistical Analysis Plan (SAP).

6.3 Populations for Analyses

Analyses will be performed as per protocol and will be fully described in the SAP. For purposes of analysis, the analysis sets in Table 9 are defined.

Table 9. Analysis Sets

Analysis Set	Description
Enrolled Set	The Enrolled Set will include all eligible participants with informed consent signed.
Exposed Set	The Exposed Set will include all participants from the Enrolled Set who received the trial vaccine.
Per Protocol Set (PPS)	The Per Protocol Set will include all participants from the Enrolled Set who received the trial intervention as per protocol, had immunogenicity results pre- and post-dose, complied with the allowed dosing/blood draw intervals, without intercurrent conditions that may interfere with immunogenicity and without prohibited concomitant medication/vaccination.
Solicited Safety Set	Solicited Safety Set will include all participants who returned the daily diary.

6.4 Data Analyses

6.4.1 General Considerations

All AE verbatim terms will be recorded and coded using the current version of Medical Dictionary for Regulatory Activities (MedDRA), 25.0 or latest. The concomitant medication will be coded using WHO Drug Dictionary (WHO DD) (last updated on 1 Sep 2020) or latest.

All computations and generation of tables, listings and data for figures will be performed using SAS® version 9.4 or higher (SAS Institute, Cary, NC, USA). The following descriptive statistics will be used as applicable to summarize the trial data:

- Continuous variables: number of non-missing values (n), mean, standard deviation (SD), median, minimum (min) and maximum (max). 95% CI of the mean may be provided as well. The number of missing values will also be provided.
- Categorical variables: frequencies, percentages and associated 95% Clopper-Pearson (exact) CIs, as applicable.

6.4.2 Planned Analyses

Analysis of primary endpoints:

The primary endpoint analysis will be performed on the Exposed Set.

The number and percentage of participants reporting solicited local (any, Grade 3, medically attended) and general (any, Grade 3, related, Grade 3 related, medical attended) AE during the follow-up period will be tabulated with exact Clopper-Pearson 95% CI.

The duration (in terms of number of days) of each solicited local and general AE during the 7-day follow-up period (Day 1 - Day 7) will be tabulated.

The number and percentage of participants reporting ongoing solicited (local and general) AEs at the end of the 7-day follow-up period will be tabulated with exact 95% CI.

Occurrence of fever will also be reported per 0.5°C cumulative increments.

The number and percentage of participants reporting at least 1 unsolicited AE (any, Grade 3, related, Grade 3 related, medically attanded) classified by the MedDRA during the 21-day follow-up period (Day 1 - Day 21) will be tabulated with exact 95% CI, overall, by MedDRA system organ class (SOC) and preferred term (PT).

The number and percentage of participants reporting at least 1 SAE during the trial period will be tabulated with exact 95% CI, overall and by MedDRA SOC and PT.

SAEs and withdrawals due to AE(s) will be described in detail in listings.

Analysis of secondary endpoints:

The secondary endpoint analysis will be performed on the PPS and Exposed Set.

- GMTs of HI titers on Days 1 and 22, with 95% CI.
- MGI at Day 22, with 95% CI.
- SCRs at Day 22, with 95% CI.
- SPRs on Day 22, with 95% CI.

6.4.3 Exploratory Analyses

Not applicable.

6.4.4 Safety Analyses

All safety analyses will be performed on the Exposed Set and Solicited Safety Set.

For the analysis of vaccine safety, the following parameters and the 95% CI will be calculated:

- The percentage of participants with at least 1 local AE (solicited and/or unsolicited), with at least 1 general AE (solicited and/or unsolicited) and with any AE during the solicited follow-up period after vaccination will be tabulated with exact 95% CI.
- The percentage of participants reporting each individual solicited local (any, Grade 3) and general (any, Grade 3, related, Grade 3 related, medically attended) AE during the solicited follow-up period after vaccination will be tabulated with exact 95% CI.
- The duration statistics (in terms of number of days) of each solicited local and general AE during the 7 day post-vaccination follow-up period will be tabulated.
- The percentage of participants reporting ongoing solicited (local and general) AEs at the end of the solicited follow-up period will be tabulated with exact 95% CI.
- Temperature will be reported per 0.5°C cumulative increments beginning with temperature 37.5°C/99.5°F.
- The percentage of participants with at least 1 report of an unsolicited AE (any, Grade 3, related, Grade 3 related) classified by the MedDRA during the follow-up period will be tabulated with exact 95% CI.
- The proportion of participants who started to receive at least 1 concomitant medication during the follow-up period will be tabulated with exact 95% CI.
- The percentage of participants with at least 1 report of SAE classified by MedDRA during the trial period will be tabulated with exact 95% CI.
- The percentage of participants with at least 1 report of a medically attended event classified by MedDRA during the trial period will be tabulated with exact 95% CI.
- SAEs and withdrawals due to AE(s) will be described in detail in Listings.

6.4.5 Handling of Missing Data

It is optimal to prevent missing data, to the extent possible, through strategies set forth in the design and conduct of a trial. For the current trial, we will aim to minimize missing information; for a given participants and a given immunogenicity measurement, missing or non-evaluable measurements will not be replaced.

The data will be analyzed as they are recorded in the trial eCRF. However, the amount of missing values for data elements will be reported. Characteristics of participants who returned and who did not return the diary card will be described.

6.4.6 Limitations of Research Methods

Some limitations can be anticipated for this trial. The trial is designed/powered to capture very common (≥1 per 10) and common (≥1 per 100 to <1 per 10) AEs. Due to its limited size the trial is not well suited to detect uncommon (≥1 per 1000 to <1 per 100), rare (≥1 per 10 000 to <1 per 1000) or very rare (<1 per 10 000) AEs.

Furthermore, as this trial aims to collect data that are self-reported and encoded by the participant, it is anticipated that limitations common to non-interventional studies that use participant-reported data may also apply to the current trial. As we expect that the majority of participants will not have a medical background, it cannot be completely ruled out that, despite instructions, the severity grade of any AEs experienced may be inaccurately reported by the vaccinees. This possibility is expected, however, to be mitigated/minimized by the straightforward definitions from the US Food and Drug Administration (FDA) AE Grading provided in the diary card.

In addition, it could be possible to face some underreporting of events, as the reporting will be solely based on the participants' willingness to complete the information in the card and return the completed card to the Investigator.

To minimize reporting bias, we will provide a pre-defined list of symptoms commonly experienced after the receipt of inactivated influenza vaccines to ease the identification and capture of symptoms experienced. In addition, the participants will be provided with the opportunity to report any other symptoms that they may experience and explicitly indicate if they have not experienced any AE to maximize the accuracy and comprehensiveness of the reporting.

6.5 Data Reporting

6.5.1 Progress Reports (if applicable)

Not applicable.

6.5.2 Annual/ Interim Analyses and Reporting (if applicable)

Not applicable.

6.5.3 Final Analyses and Reporting

A final trial report will be generated after all data collection is complete, including up to 21 days of follow-up for all enrolled participants. The final report will encompass all planned analyses, including a description of the complete trial population, as described above and in the SAP.

7. STUDY MANAGEMENT

This trial will be performed by IQVIA with guidance, input, review and approval of GSK, including development of materials, recruitment, training and management of sites, electronic data capture (EDC) and data management and analysis.

7.1 Data Entry/ Electronic Data Capture

All data will be collected and entered directly into the EDC system. All participating sites will have access to the data entered regarding the individual site its own enrolled participants. All sites will be fully trained in using the online data capture system, including eCRF completion guidelines and help files. Sites will be responsible for entering extracted participant data into a secure internet-based EDC registry database via the eCRF. Investigators and site personnel will be able to access their account with a username and password. All eCRFs should be completed by designated, trained personnel or the trial coordinator, as appropriate. All the eCRFs should be reviewed, electronically signed, and dated by the Principal Investigator. All changes or corrections to eCRFs are documented in an audit trail and an adequate explanation is required.

7.2 Compensation

Not applicable.

7.3 Source Documents

Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Investigators should maintain a record of the location(s) of their source documents. Data entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The Investigator may need to request previous medical records or transfer records, depending on the trial. Also, current medical records must be available. The source documents will include diary card, laboratory reports and any medical records of individual participants. All original source documentation is expected to be stored at the site for 15 years as required by applicable local regulations.

7.4 File Retention and Archiving

To enable evaluations and/or audits from regulatory authorities or the GSK, the Investigator agrees to keep records, including the identity of all participating participants, all original signed informed consent forms (ICFs), copies of all case report forms (CRFs), SAEs forms, source documents and adequate documentation of relevant correspondence (e.g., letters, meeting minutes, telephone calls reports). The records should be retained by the Investigator according to local regulations, or as specified in the trial contract, whichever is longer.

Each site will receive a trial site file at trial initiation which contains all documents necessary for the conduct of the trial and is updated throughout the trial. This file must be available for review in the event the site is selected for monitoring, audits, or inspections and must be safely archived for at least 15 years after the completion of participation in the trial. Documents to be archived include the participant enrollment log and the signed ICF. In the event that archiving of the file is no longer possible at the site, the site will be instructed to notify the Sponsor.

7.5 Quality Assurance and Monitoring

The Investigator will maintain a record of the location(s) of their respective essential documents including source documents. The storage system used during the trial and for archiving (irrespective of the type of media used) will provide for document identification, version history, search, and retrieval.

Essential documents for the trial may be added or reduced where justified (in advance of trial initiation) based on the importance and relevance to the trial. When a copy is used to replace an

original document (e.g., source documents, CRF), the copy will fulfill the requirements for certified copies.

All participant data relating to the trial will be recorded on printed or electronic CRF unless transmitted to the Sponsor or designee electronically (e.g., laboratory data). The Investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the eCRF.

The Investigator must maintain adequate and accurate source documents and trial records that include all pertinent observations on each of the site's trial participants that support the information entered in the eCRF.

The Investigator must permit trial-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source documents or certified copies.

The Sponsor or designee is responsible for the data management of this trial, including quality checking of the source data.

To ensure compliance with Good Clinical Practice (GCP) or other applicable guidelines and all applicable regulatory requirements, GSK may conduct a QA audit. Regulatory agencies may also conduct a regulatory inspection of this trial. Such audits/inspections can occur at any time during or after completion of the trial. If an audit or inspection occurs, the database owner and institution agree to allow the auditor/inspector direct access to all relevant documents and to allocate his/her time and the time of his/her staff to the auditor/inspector to discuss findings and any relevant issues.

Trial monitors will perform ongoing source data verification to confirm that data entered into the eCRF by authorized site personnel are attributable, legible, contemporaneous, original, accurate, and complete. Changes to source data should be traceable, should not obscure the original entry, and should be explained if necessary (e.g., via an audit trail). Safety and rights of participants must be protected, and the trial should be conducted in accordance with the currently approved protocol and any other trial agreements, International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) GCP, and all applicable regulatory requirements.

GSK will inform the Investigator/institution of the time period for retaining these records to comply with all applicable regulatory requirements. However, the Investigator/institution should

seek the written approval of the Sponsor before proceeding with the disposal of these records. The minimum retention time will meet the strictest standard applicable to a particular site, as dictated by ICH GCP or other applicable guidelines, any institutional requirements or applicable laws or regulations, or GSK standards/procedures; otherwise, the retention period will default to 15 years from the date of completion of study report/equivalent summary.

A trial monitoring plan, including for-cause monitoring, that is appropriate for the trial design will be developed and implemented.

7.6 Data Management

A data management plan (DMP) will be created before data collection begins and will describe all functions, processes, and specifications for data collection, cleaning, and validation. The eCRFs will include programmable edits to obtain immediate feedback if data are missing, out-of-range, illogical or potentially erroneous. Concurrent manual data review will be performed based on parameters dictated by the plan. Ad hoc queries will be generated within the EDC system and followed up for resolution.

High data quality standards will be maintained, and processes and procedures utilized to repeatedly ensure that the data are as clean and accurate as possible when presented for analysis. Data quality will be enhanced through a series of programmed data quality checks that automatically detect out-of-range or anomalous data.

7.7 Changes to the Protocol

Changes to the protocol will be documented in written protocol amendments. Major (i.e., substantial, significant) amendments will usually require submission to the relevant IRB/ IECs for approval or favorable opinion. In such cases, the amendment will be implemented only after approval or favorable opinion has been obtained.

Minor (non-substantial) protocol amendments, including administrative changes, will be filed by at each participating site and will be submitted to the relevant IRB/ IEC or regulatory authorities where required by pertinent regulations. Any amendment that could have an impact on the participant's agreement to participate in the trial requires the participant's informed consent prior to continued participation in the trial.

7.8 Study Governance

Not applicable

7.9 Publication Policy

Trial information from this protocol will be posted on applicable publicly available clinical trial registers before enrolment of participants begins.

Summaries of the results of GSK interventional studies (Phase I-IV) are posted on applicable publicly available results registers within 12 months of the primary completion date for studies of authorized vaccines

GSK also aims to publish the results of these studies in searchable, peer reviewed scientific literature. Manuscripts are submitted for publication within 24 months of the last participant's last visit.

8. SAFETY REPORTING

The Investigator or site staff is/are responsible for the detection, documentation and reporting of events meeting the criteria and definition of an AE or SAE as provided in this protocol.

Each participant will be instructed to contact the Investigator immediately should he/she experience any signs or symptoms he/she perceives as serious.

8.1 Definitions

Adverse events (AEs)

An AE is any untoward medical occurrence in a clinical investigation participant, temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

A SAE is any untoward medical occurrence that:
a. Results in death.
b. Is life-threatening.

Note: The term 'life-threatening' in the definition of 'serious' refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, had it been more severe.
c. Requires hospitalization or prolongation of existing hospitalization Note: In general, hospitalization signifies that the participant has been admitted at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or in an outpatient setting. Complications that occur during hospitalization are also considered as AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event will also be considered serious. When in doubt as to whether 'hospitalization' occurred, or was necessary, the AE should be considered serious.
d. Results in disability/incapacity Note: The term disability means a substantial disruption of a person's ability to conduct normal life functions. This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza like illness, and accidental trauma (e.g. sprained ankle) which may interfere or prevent everyday life functions but do not constitute a substantial disruption.
e. Is a congenital anomaly/birth defect in the offspring of a trial participant.
f. Abnormal pregnancy outcomes (e.g. spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy).
g. Other situations Medical or scientific judgment should be exercised in deciding whether reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These should also be considered serious. Examples of such events are invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization.

8.2 Procedures for Reporting Adverse Events in the CRF

All AEs (serious and non-serious) reported during the follow-up period will be captured on the eCRF. Each suspected AE occurring during the trial must be recorded in the eCRF and/or specific AE forms as designated by the GSK, including the description, seriousness criteria, severity,

duration (onset and resolution date), causal relationship with the trial treatment, actions taken with the trial treatment (withdrawal), any other required treatment, and outcome.

The outcome of each AE (serious or non-serious) should be entered with a term such as those described below:

- Recovered/Resolved
- Recovering/Resolving
- Not Recovered/Not Resolved
- Recovered/Resolved with Sequelae
- Fatal

If any of the same AEs occur on several occasions in the same participant, then the AE in question must be documented and assessed each time. In cases of surgical or diagnostic procedures, the condition/ illness leading to such a procedure is considered as the AE rather than the procedure itself.

8.3 Procedures for Reporting Adverse Events to GSK Drug Safety

In addition to recording the event on the eCRF, all SAEs and non-serious AEs considered related to *Fluarix Tetra* reported during follow-up must also be reported to IQVIA and GSK Pharmacovigilance for purposes of regulatory reporting. Site personnel must complete and submit the appropriate SAE report form (available through the EDC system) and forward it to IQVIA and GSK Pharmacovigilance within 24 hours of becoming aware of the event. To ensure participant safety, all SAEs and non-serious AEs considered related to *Fluarix Tetra* occurring after informed consent is signed and until 21days after last exposure to the product, should be reported to IQVIA and GSK Pharmacovigilance within 24 hours of learning of its occurrence.

All completed SAE forms should be sent to:

IQVIA Drug Safety	Email: QLS_Fluarix_SO@iqvia.com Fax: + 001 919 800-0122 Telephone: + 0091 80 71311011

In order to maintain compliance with the Indian and other regulatory bodies, Investigator may be further contacted by GSK Pharmacovigilance in order to collect additional information required to evaluate the potential event. AEs/ SAEs will be reported to local and regional health authorities by the Sponsor, when appropriate, in accordance with applicable local and regional regulations. The Investigator is responsible for maintaining compliance with any applicable site-specific requirements related to the reporting of SAEs or other safety information to the local IRB/ IEC that approved the trial.

Study contact for reporting vaccine related SAEs in case the eCRF reporting system does not work
24/24 hour and 7/7 day availability: GSK Clinical Safety & Pharmacovigilance Fax: +32 2 656 51 16 or +32 2 656 80 09 Email address: PV.ICSRManagement@gsk.com

8.4 Procedures for Reporting Pregnancies (If Applicable)

Not applicable.

8.5 Procedures for Reporting Product Complaints and Medication Errors (If Applicable)

Not applicable.

9. ETHICAL AND REGULATORY CONSIDERATIONS

9.1 Guiding Principles

To ensure the quality and integrity of research, this trial will be conducted under the GCP, the GPPs issued by the International Society for Pharmacoepidemiology (ISPE), the Declaration of Helsinki (DOH) and its amendments, ICH GCP, New Drugs and Clinical Trial Rules, 2019 and applicable national guidelines.

9.2 Required Documents

Prior to the enrollment of any participant in the trial, the following documents must be provided by the site to the GSK:

- Copy of the IRB/ IEC approval letter for the protocol and informed consent (all written information provided to the participant must be approved by the IRB/IEC)
- Copy of the IRB/ IEC-approved informed consent document to be used
- Copy of the protocol signoff page signed by the Investigator
- Fully executed Clinical Trial Agreement

9.3 Participant Information and Informed Consent

Please refer appendix 1 - ANNEX 1 (Section Informed Consent Process)

9.4 Participant Confidentiality

In order to maintain participant confidentiality, each participant will be assigned a unique participant identifier upon trial enrolment. This participant identifier will be used in place of participant name for the purpose of data analysis and reporting. Medical record numbers or other local reference identifiers are not collected as part of the database. However, race and ethnicity information will be collected as a part of demographics to determine the diversity in the clinical trial participation. All parties will ensure protection of participant personal data and will not include participant names on any trial forms, reports, publications, or in any other disclosures, except where required by law. In accordance with local regulations, participants will be informed about data handling procedures and asked for their consent. Data protection and privacy regulations will be observed in capturing, forwarding, processing, and storing participant data. Participant confidentiality will be strictly maintained.

The database will be housed at the IQVIA in a physically and logically secure computer system maintained by the IQVIA in accordance with a written security policy. The system meets approved established standards for the security of health information and is validated. The system also meets the standards of the ICH guideline E6 R2 regarding electronic trial data handling and is available for audit upon request.

9.5 Independent Ethics Committee/ Institutional Review Board

Consistent with local regulations and prior to enrollment of participants at a given site, the trial protocol will be submitted together with its associated documents (e.g., ICF) to the responsible IRB/ IEC for its review. Participant enrollment will not start at any site before the written confirmation of a favorable opinion/ approval from the relevant central or local IRB/ IEC. The IRB/ IEC will be asked to provide documentation of the date of the meeting at which the favorable opinion/ approval was given that clearly identifies the trial, the protocol version, and the ICF version reviewed.

Before implementation of any substantial changes to the protocol, protocol amendments will also be submitted to the relevant IRB/ IEC in a manner consistent with local regulations. Pertinent safety information will be submitted to the relevant IECs during the course of the trial in accordance with local regulations and requirements. It is the responsibility of the Investigator to have prospective approval of the trial protocol, protocol amendments, and ICFs, and other relevant documents, if applicable, from their local IRB/ IEC and provide documentation of approval to IQVIA. All correspondence with the IRB/ IEC should be retained in the Investigator File.

Should the trial be terminated early for any unanticipated reason, the Investigator will be responsible for informing the IRB/ IEC of the early termination.

10. REFERENCES

- Barr G, Jelley LL. The coming era of quadrivalent human influenza vaccines: who will benefit? Drugs. 2012;72(17):2177-85.
- Clinical Review, Fluarix Quadrivalent, GlaxoSmithKline Biologicals.
- Clopper CJ, Pearson ES. The use of confidence or fiducial limits illustrated in the case of the binomial. Biometrika 1934;26:404-13.
- Dangi, T., Jain, A. Influenza Virus: A Brief Overview. Proc. Natl. Acad. Sci. India Sect B. Biol. Sci. 2012;82(1):111–121.
- Fluarix Tetra vaccine US Prescribing information, revised in 2021.
- Iuliano AD, Roguski KM, Chang HH, et al. Estimates of global seasonal influenza-associated respiratory mortality: a modelling study. Lancet. 2018;391:1285-300.
- Guidance for Industry Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials. Available at https://www.fda.gov/media/73679/download. Accessed: June 5, 2022.
- Kieninger D, Sheldon E, Lin WY, et al. Immunogenicity, reactogenicity and safety of an inactivated quadrivalent influenza vaccine candidate versus inactivated trivalent influenza vaccine: a phase III, randomized trial in adults aged ≥18 years. BMC Infect Dis. 2013;13:343.
- Narayan VV, Iuliano AD, Roguski K, et al. Burden of influenza-associated respiratory and circulatory mortality in India, 2010-2013. J Glob Health. 2020;10(1).
- Wright PF, Neumann G, Kawaoka Y. Orthomyxoviruses. In: Knipe DM, Howley PM, editors. Fields Virology. 5th Philadelphia, PA: Lippincott Williams & Wilkins; 2007:1691-740.
- CDC, 2023. 2022-2023 U.S. Flu Season: Preliminary In-Season Burden Estimates. centers for disease control and prevention. Available at https://www.cdc.gov/flu/about/burden/preliminary-in-season-estimates.htm. Accessed: April 10, 2023.
- WHO 2023. Recommendations announced for influenza vaccine composition for the 2023-2024 northern hemisphere influenza season. Available at https://www.who.int/news/item/24-02-2023-recommendations-announced-for-influenza-vaccine-composition-for-the-2023-2024-northern-hemisphere-influenza-season. Accessed: April 10, 2023.

11. APPENDICES

ANNEX 1 REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS

Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and with the following:
  - Consensus ethical principles derived from international guidelines including the DOH and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines.
  - Applicable ICH GCP Guidelines.
  - Applicable laws and regulations.
- The protocol, protocol amendments, ICF, and other relevant documents (e.g., advertisements) must be submitted to an IRB/ IEC by the Investigator and reviewed and approved by the IRB/ IEC before the study is initiated.
- Any amendments to the protocol will require IRB/ IEC and regulatory authority approval, when applicable, before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to participants.
- The Investigator will be responsible for the following:
  - Providing written summaries of the status of the study to the IRB/ IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC.
  - Notifying the IRB/ IEC of SAEs or other significant safety findings as required by IRB/ IEC procedures.
  - Providing oversight of the conduct of the study at the study center and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC for clinical studies (if applicable), and all other applicable local regulations.

Financial Disclosure

Investigators and sub-Investigators will provide the Client with sufficient, accurate financial information as requested to allow the GSK to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study.

Insurance

IQVIA/GSK will obtain liability insurance, which covers this study as required by local law and/or national regulations and/or ICH guidelines, whichever is applicable. The terms of the insurance will be kept in the study files.

Informed Consent Process

- The Investigator or his/her representative must fully explain the nature of the trial including the risks and benefits, to the participant or their care giver and answer all questions regarding the trial.
- Participants must be informed that their participation is voluntary.
- Freely given and written informed consent must be obtained from each participant, as appropriate, prior to participation in the trial.
- Participant or their legally authorized representative will be required to sign a statement of informed consent that meets the requirements of local regulations, ICH guidelines, privacy, and data protection requirements, where applicable, and the IRB/ IEC or study center.
- The medical records must include a statement that written informed consent was obtained before the participant was enrolled in the trial and the date when the consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- Participants must be re-consented if a new version of the ICF(s) or an ICF addendum is released during their participation in the trial.
- A copy of the ICF(s) must be provided to the participants.

Administrative Structure

Not applicable.

Medical Monitor

PPD

PPD

Dissemination of Clinical Study Data

- The key design elements of this protocol and results summaries will be posted on GSK Clinical Study register in compliance with the applicable regulations/GSK policy according to the timelines described below.
- Protocol summaries will be registered prior to study start.
- Results summaries will be posted within 12 months of analysis completion date.
- Where required by regulation, summaries will also be posted on applicable national or regional clinical trial registers.

Where required by applicable regulatory requirements, an Investigator signatory will be identified for the approval of the study report, and provided reasonable access to statistical tables, figures, and relevant reports. GSK will also provide the Investigator with the full summary of the study results. The Investigator is encouraged to share the summary results with the study participants, as appropriate.

Data Quality Assurance

- All participant data relating to the study will be recorded on eCRFs unless transmitted to the Client or designee electronically (e.g., laboratory data). The Investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.
- The Investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF.
- The Investigator must permit study-related monitoring, audits, IRB/ IEC review, and regulatory agency inspections and provide direct access to source data documents.
- GSK is responsible for the data management of this study including quality checking of the data.
- Study monitors will perform ongoing source data verification to confirm that data entered into the eCRF by authorized study center personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.
- Details of study monitoring, including action required due to SARS-CoV-2 (COVID-19), will be included in a separate Study Monitoring Plan.

- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the Investigator for 15 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the Client. No records may be transferred to another location or party without written notification to the Client.

Source Documents

The Investigator should maintain a record of the location(s) of their respective essential documents including source documents. The storage system used during the study and for archiving (irrespective of the type of media used) should provide for document identification, version history, search, and retrieval.

Essential documents for the study may be added or reduced where justified (in advance of study initiation) based on the importance and relevance to the study. When a copy is used to replace an original document (e.g., source documents, CRF), the copy should fulfill the requirements for certified copies.

All participant data relating to the study will be recorded on electronic CRF unless transmitted to the Sponsor or designee electronically (e.g., laboratory data). The Investigator is responsible for verifying that data entries are accurate and correct by electronically signing the electronic case report form (eCRF).

The Investigator must maintain adequate and accurate source documents and study records that include all pertinent observations on each of the site's study participants that support the information entered in the eCRF.

The Investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source documents or certified copies.

The Sponsor or designee is responsible for the data management of this study including quality checking of the source data.

Study monitors will perform ongoing source data verification to confirm that data entered into the eCRF by authorized site personnel are attributable, legible, contemporaneous, original, accurate, and complete. Changes to source data should be traceable, should not obscure the original entry, and should be explained if necessary (e.g., via an audit trail). Safety and rights of participants must

be protected, and study be conducted in accordance with the currently approved protocol and any other study agreements, and all applicable regulatory requirements.

Quality tolerance limits (QTLs) will be pre-defined to identify systematic issues that can impact participant safety and/or reliability of study results. These pre-defined parameters will be monitored during the study and important deviations from the QTLs and remedial actions taken will be summarized in the study report.

GSK will inform the Investigator/institution of the time period for retaining these records to comply with all applicable regulatory requirements. However, the Investigator/ institution should seek the written approval of GSK before proceeding with the disposal of these records. The minimum retention time will meet the strictest standard applicable to a particular site, as dictated by ICH GCP or other applicable guidelines, any institutional requirements, applicable laws or regulations, or GSK standards/procedures. Otherwise, the retention period will default to 15 years from the date of completion of study report/equivalent summary.

Study and Study Center Closure

GSK or its designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of GSK, provided there is sufficient notice given to account for participant's safe exit from study. Study sites regular closure will occur upon study completion. A study site is considered closed when all required data/documents and study supplies have been collected and a study site closure visit has been performed.

The Investigator may initiate study site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the Sponsor or Investigator may include but are not limited to:

- Failure of the Investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the Sponsor's procedures
- Inadequate recruitment of participants by the Investigator
- Total number of participants included earlier than expected

Publication Policy

The data generated by this study are confidential information of the GSK. The GSK will make the results of the study publicly available. The publication policy with respect to the Investigator and study center will be set forth in the Clinical Trial Agreement.

The following information is required by ICH to be in the protocol if not addressed in another document. If not addressed in the Clinical Trial Agreement, use the following example text, and modify as needed:

The results of this study may be published or presented at scientific meetings. If this is foreseen, the Investigator agrees to submit all manuscripts or abstracts to GSK before submission. This allows the GSK to protect proprietary information and to provide comments.

- The GSK will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, GSK will generally support publication of multi-center studies only in their entirety and not as individual study center data. In this case, a Coordinating Investigator will be designated by mutual agreement.
- Authorship will be determined by mutual agreement and in line with the International Committee of Medical Journal Editors' authorship requirements.

Electronic Signature Manifestation

This page is a manifestation of the electronic signature(s) used in compliance with the organization's electronic signature policies and procedures.

Signer Full Name	Meaning of Signature	Date and Time
PPD	Document Approval (I certify that I have the education, training and experience to perform this task)	05 May 2023 16:36:19 UTC
PPD	Document Approval (I certify that I have the education, training and experience to perform this task)	05 May 2023 16:38:00 UTC