CONVENIO ESPECÍFICO DE COLABORACIÓN ENTRE LA CONSELLERÍA DE SANIDAD, EL SERVICIO GALLEGO DE SALUD Y LA FUNDACIÓN INSTITUTO DE INVESTIGACIÓN SANITARIA DE SANTIAGO DE COMPOSTELA (FIDIS) PARA LA REALIZACIÓN EN GALICIA DEL ENSAYO CLÍNICO ALEATORIZADO, PRAGMÁTICO, PARA EVALUAR LA EFICACIA DE LA VACUNA ANTIGRIPAL TETRAVALENTE DE DOSIS ALTA FRENTE A LA VACUNA ANTIGRIPAL TETRAVALENTE DE DOSIS ESTÁNDAR EN ADULTOS DE 65 A 79 AÑOS (GALFLU: CLINICAL ASSAY)

Santiago de Compostela, fecha de la última firma electrónica.

REUNIDOS

De una parte, don Julio García Comesaña, conselleiro de Sanidad y presidente del Servicio Gallego de Salud, de acuerdo con lo establecido en el artículo 34 de la Ley 1/1983, de 22 de febrero, de normas reguladoras de la Xunta y de su Presidencia, y de conformidad con los Decretos 136/2019, y 137/2019, de 10 de octubre, por los que se establecen las estructuras orgánicas de la Consellería de Sanidad y del Servicio Gallego de Salud, respectivamente, así como con lo establecido en la Ley 1/2016, de 18 de enero, de transparencia y buen gobierno de Galicia, y en la Ley 40/2015, de 1 de octubre, de régimen jurídico del sector público.

De otra parte, Dña. Isabel Lista García, en calidad de Directora de la Fundación Instituto de Investigación Sanitaria de Santiago de Compostela (FIDIS), con CIF G15796683 y domicilio en Travesía da Choupana s/n, 15706 en Santiago de Compostela.

Las partes manifiestan tener y se reconocen, mutua y recíprocamente, la capacidad necesaria para otorgar el presente documento, a cuyos efectos

EXPONEN

Primero.- El profesor doctor don Federico Martinón Torres, jefe del Servicio de Pediatría del Hospital Clínico Universitario de Santiago de Compostela es el promotor e investigador principal del "*Ensayo clínico aleatorizado, pragmático, para evaluar la eficacia de la vacuna antigripal tetravalente de dosis alta frente a la vacuna antigripal tetravalente de dosis estándar en adultos de 65 a 79 años en Galicia, España*" (Ensayo clínico "GALFLU").

A través de dicho ensayo se pretende evaluar la eficacia de la vacuna QIV-HD respecto a la QIV-SD en la reducción del riesgo de hospitalización debido a problemas cardio respiratorios o neumonia por gripe en personas de 65 a 79 años, durante la campaña de vacunación 2023/2024 y 2024/2025. Este estudio pretende informar a su vez a la Dirección General de Salud Pública de la Consellería de Sanidad sobre la utilidad de la vacunal QIV-HD también en

este tramo de edad y la eventual necesidad de modificar las recomendaciones actuales que contemplan su administración a partir de los 80 años.

Todas las personas en ese rango de edad que vayan a recibir la vacuna de la gripe como parte del programa gallego de vacunación anual serán invitadas a participar en el estudio. Se espera que en este estudio participen en Galicia 114.000 personas de edad comprendida entre 65 y 79 años,

En el contexto del estudio se administrarán los 2 tipos de vacuna frente a la gripe, de alta dosis y de dosis estándar, cada persona tiene un 50% de posibilidades de recibir una u otra vacuna. El hecho de recibir una vacuna u otra vendrá determinado por el azar.

Según se establece en el apartado 10.3. del Protocolo del ensayo (versión 1.0. del 5 de junio de 2023), elaborado conjuntamente por el promotor del ensayo y por SANOFI, todas las dosis de vacunas QIV-HD que se utilicen en el ensayo clínico GALFLU, unas 27.000 dosis por cada una de las 2 temporadas de vacunación durante las cual se realizará el ensayo, serán facilitadas por SANOFI, quien asumirá la totalidad de los costes que se deriven del ensayo, incluido el coste de la totalidad de las dosis de vacuna empleadas.

Segundo.- El párrafo 3º del artículo 58.1 del Real Decreto Legislativo 1/2015, de 24 de julio, por el que se aprueba el texto refundido de la Ley de garantías y uso racional de los medicamentos y productos sanitarios, relativo a los "*Ensayos clínicos y estudios observacionales*", establece que:

> "*Las autoridades sanitarias deberán facilitar la realización de los ensayos clínicos en el Sistema Nacional de Salud, tanto en el ámbito de la atención primaria como de la hospitalaria. Las condiciones de desarrollo de los ensayos clínicos en los servicios sanitarios del Sistema Nacional de Salud se establecerán en virtud de los acuerdos que se establezcan entre el promotor y los servicios de salud de las comunidades autónomas con criterios de transparencia y según lo establecido en esta ley. Dichos acuerdos incluirán todos los aspectos necesarios para la correcta realización del ensayo, incluidos los profesionales participantes, los recursos implicados y las compensaciones que se establezcan.*".

Tercero.- La Consellería de Sanidad, a través da Dirección General de Salud Pública, tiene entre sus objetivos la prevención, promoción y protección colectiva de la salud de la población gallega y el desarrollo de programas sanitarios en materia de salud pública. Este órgano directivo tiene adscrita ademas la Escuela Gallega de Salud Pública, creada mediante el Decreto 86/2022, de 19 de mayo, por el que se establecen la creación y el marco normativo regulador de las actividades de la Escuela Gallega de Salud Pública, como una iniciativa orientada a fomentar la formación e investigación científica en materia de salud pública necesaria para dar respuesta a los desafíos y peligros para la salud de la población y ante amenazas sanitarias globales. Las actividades que integran la Escuela Gallega de Salud Pública se llevarán a cabo, entre otras cosas, con la finalidad de desarrollar un proceso continuo de innovación y actualización del conocimiento en salud pública en el ámbito de la investigación en materia de salud pública, así como de crear nuevos espacios de intercambio y circulación de la información, fomentando la construcción de redes intersectoriales que faciliten la transferencia de conocimiento entre las personas que lo necesitan y las que lo generan.

Entre sus actividades, recogidas en el artículo 3.1 del Decreto 86/2022, de 19 de mayo, destacan las siguientes:

"e) e) Definir y fomentar la investigación en salud pública por su capacidad innegable para poner en valor las actuaciones que se realizan o para identificar nuevas estrategias a llevar a cabo, creando una red de investigación en salud pública que favorezca la generación y transferencia de conocimientos, preste apoyo a los profesionales, promueva el trabajo en equipo y cree alianzas entre los diferentes organismos implicados en la salud.

f) Promover colaboraciones con las universidades y con otras escuelas o entidades de formación y/o investigación.

g) Fomentar la colaboración con las diferentes administraciones, instituciones, organismos, sociedades científicas o empresas en relación con la formación e investigación en salud pública, con base en los correspondientes acuerdos o convenios de colaboración que se establezcan".

Cuarto.- La Ley 1/1989, de 2 de enero, creó el Servicio Gallego de Salud como un organismo autónomo de carácter administrativo, dotado de personalidad jurídica propia, que tiene como finalidad la gestión de los servicios sanitarios de carácter público dependientes de la Comunidad Autónoma de Galicia y la coordinación integral de todos los recursos sanitarios y asistenciales.

Quinto.- La Ley 8/2008, de 10 de julio, de sanidad de Galicia, en su disposición adicional primera, relativa al "*Sistema integrado de información de la investigación clínica del Sistema Público de Salud de Galicia*", añadida por el artículo 34 de la Ley 18/2021, de 27 de diciembre, de modificación de la Ley 8/2008, del 10 de julio, entre otros, establece que:

"1. La consejería competente en materia de sanidad pondrá en marcha un Sistema integrado de información de la investigación clínica del Sistema Público de Salud de Galicia que dé cobertura a todos los centros que lo componen, con la finalidad de aprovechar las sinergias en investigación clínica y facilitar y fomentar la incorporación de terapias innovadoras en fases tempranas de desarrollo.

2. En la implantación de este sistema se adoptarán todas las medidas tecnológicas, organizativas y de seguridad que sean necesarias para garantizar el cumplimiento de la legislación sectorial específica y sobre protección de datos, así como para mejorar la coordinación de las actuaciones desarrolladas en la gestión de las actividades de investigación y proporcionar mayor valor a sus resultados.

Sexto.- La Fundación Instituto de Investigación Sanitaria de Santiago de Compostela (FIDIS) es una entidad sin ánimo de lucro que persigue fines de interés general, y que tiene como objeto impulsar la investigación, la docencia, el desarrollo científico tecnológico y la innovación en el ámbito sanitario y en ciencias de la salud y que se encuentra incluida entre

las entidades beneficiarias del mecenazgo relacionadas en el artículo 16 de la Ley 49/2002, de 23 de Diciembre, de régimen fiscal de las entidades sin fines lucrativos y de los incentivos fiscales al mecenazgo.

Séptimo.- Que el 26.03.2021 la Consellería de Sanidad y la FIDIS subscribieron el "*Convenio marco de colaboración entre la Conselleria de Sanidad de la Xunta de Galicia y el Grupo de Investigación en Vacunas e Infecciones (GENVIP) del Instituto de Investigacion Sanitaria de Santiago para la investigación aplicada en infecciones y vacunas en Galicia.*". Este convenio tiene un duración de cuatro años, contados desde el día de su firma, prorrogables por un máximo de cuatro más, previa formalización por escrito de la correspondiente prórroga.

Según se recoge en la cláusula primera de dicho convenio, relativa al "*Objeto del convenio*", su objeto es:

> "*1 ….establecer el marco adecuado que facilite y fomente el desarrollo de un plan de colaboración en análisis e investigación para aplicar las últimas tecnologías de investigación disponibles y profundizar en el análisis exhaustivo de la información epidemiológica de enfermedades infecciosas y aplicación de vacunas en Galicia, utilizando procedimientos estadísticos-bio-informáticos de última generación. Así mismo, a través de un abordaje "ómico" integral, se avanzará en la comprensión de los mecanismos inmunológicos que subyacen a la protección inducida por las vacunas, se estudiarán los potenciales eventos adversos producidos por las mismas y posibles fallos vacunales en el contexto del programa de vacunación de Galicia, apoyándose en la experiencia del Centro Colaborador de la Organización Mundial de la Salud (OMS) en Seguridad Vacunal de Santiago y el Instituto de Investigación Sanitaria de Santiago.*
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> *2 Este convenio establece el marco de la colaboración entre las diferentes partes implicadas y ampara el intercambio de información y recursos con el fin de fomentar la investigación aplicada en infecciones y vacunas y que resulten de mutuo interés.*
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> *3 Las Partes se comprometen, fieles a su compromiso social, a contribuir decisivamente en la creación de un entorno facilitador que posibilite la potenciación de la investigación biomédica.*
>
> *4 Mediante documentos individualizados formalizados entre las dos instituciones se establecerán acuerdos específicos de colaboración para la realización de proyectos de investigación que contemplen las correspondientes aportaciones de recursos para la actividad a realizar. ".*

Octavo.- A través del presente convenio específico se trata de articular la colaboración entre las partes firmantes para la realización, en el ámbito del Sistema Público de Salud de Galicia, del Ensayo clínico "*GALFLU*", así como regular los compromisos y obligaciones que asumen tanto las partes conveniantes como cualquier otra persona física o jurídica que pueda colaborar o cooperar en el desarrollo o gestión del presente convenio específico o del convenio marco en el que se fundamenta, de acuerdo con lo previsto en la cláusula segunda de dicho convenio marco.

Por todo lo expuesto, las partes acuerdan suscribir el presente convenio específico, que se regirá por las siguientes:

CLÁUSULAS

Primera.- Objeto del convenio

El objeto del presente convenio específico es establecer la colaboración entre la Consellería de Sanidad, el Servicio Gallego de Salud y la Fundación Instituto de Investigación Sanitaria de Santiago de Compostela (FIDIS) para la realización en Galicia del ensayo clínico aleatorizado, pragmático, para evaluar la eficacia de la vacuna antigripal tetravalente de dosis alta frente a la vacuna antigripal tetravalente de dosis estándar en adultos de 65 a 79 años (GALFLU: CLINICAL ASSAY).

Segunda.- Promotor del ensayo

El promotor del ensayo clínico GALFLU es el Dr. D. Federico Martinón Torres, jefe del Servicio de Pediatría del Complejo Hospitalario Universitario de Santiago de Compostela.

Tercera.- Compromisos de las partes

1. La Consellería de Sanidad directamente o a través de la Dirección General de Salud Pública, u órgano que esta determine, se compromete a:

1.1. Informar del ensayo a través de sus aplicaciones informáticas, plataformas informáticas y redes sociales, así como en su caso las de sus organismos y centros dependientes. Dicha información se proporcionará mediante anuncios o mensajes de texto dirigidos a las personas (pacientes) que, cumpliendo los requisitos para participar en el mismo, puedan estar interesadas en ello. Dicha información se facilitará igualmente a las entidades que representen los intereses de dichas personas.

En la página web del Programa Gallego sobre Vacunación contra la Gripe estará disponible información detallada sobre el ensayo clínico GALFLU, desde la que se podrá acceder y descargar el modelo de consentimiento informado aprobado para el ensayo, en gallego, castellano, braille y formato audio.

Asimismo se facilitará un número de contacto telefónico al que se puedan dirigir las personas interesadas en participar en el ensayo, o las personas o entidades que representen sus intereses, a efectos de dar respuesta a las dudas que puedan tener en relación al ensayo o a su posible participación en el mismo, así como cualquier otra información que sobre el ensayo puedan precisar.

1.2. Proporcionar y equipar, con la supervisión por parte del promotor del ensayo, los puntos de vacunación en los que se vayan a vacunar las personas (pacientes) que participen en el ensayo clínico GALFLU. La preparación y el equipamiento

de los puntos de vacunación utilizados para la realización del ensayo se hará de acuerdo con la normativa que resulte de aplicación a dichos puntos, así como con lo indicando en el protocolo y, en su caso, con el resto de documentación que forme parte del expediente administrativo correspondiente al ensayo, en todo aquello que resulte de aplicación.

Para ello, las personas responsables de la Dirección General de Salud Pública, a través de las gerencias de las áreas sanitarias del Servicio Gallego de Salud, realizarán todas las gestiones y comunicaciones necesarias para la preparación y dotación del equipamiento necesario en los siguientes puntos de vacunación:

• Recinto Feiral Expocoruña- IFECO (A Coruña).

• Hospital Virxen Da Xunqueira (Cee).

• Feira De Mostras Do Noroeste - FIMO (Ferrol).

• Hospital Publico Da Mariña (A Mariña)

• Hospital Lucus Augusti (Lugo)

• Anexo IES Rio Cabe (Monforte)

• Hospital Comarcal Valdeorras (O Barco)

• Complexo Hospitalario De Ourense/ Recinto Feiral Expourense (Ourense)

• Hospital Verin (Verin)

• Edificio Administrativo Da Xunta Campolongo (Pontevedra)

• Pavillon FEXDEGA (Salnés)

• Hospital Da Barbanza (Barbanza)

• Sala Eisenman- Cidade Da Cultura (Santiago de Compostela)

• Recinto Feiral Vigo- IFEVI (Vigo)

1.3. Prestar conformidad al documento en el que se establezcan las condiciones y obligaciones del encargado de tratamiento de datos del ensayo.

1.4. Facilitar el acceso a los datos contenidos en el registro de actividades de tratamiento de la Consellería de Sanidad y del Servicio Gallego de Salud en su condición de responsable del sistema de información del Sistema Público de Salud de Galicia, correspondientes a: :

- Gestión de Historia Clínica y Actividad asistencial
- Identificación usuarios y profesionales del sistema público sanitario
- Sistema de información y vigilancia de problemas de salud pública
- Registros sanitarios

Cada uno de esos registros se utilizará para la recogida del tipo de datos que en los mismos se incluyen y, en todo caso, de aquellos que para cada registro se indican en el protocolo del ensayo y, en lo que resulte de aplicación, de la documentación anexa al mismo.

2. La Fundación Instituto de Investigación Sanitaria de Santiago de Compostela (FIDIS) se compromete a:

2.1. Facilitar la gestión del ensayo y la colaboración y la coordinación entre los distintos centros, entidades y servicios sanitarios que participen en el ensayo.

2.2. Compartir con la Consellería de Sanidad y con el Servicio Gallego de Salud los resultados obtenidos tras la realización y evaluación del ensayo.

2.3. Llevar a cabo la gestión y las labores de seguimiento de la ejecución del Convenio, lo que incluye la coordinación con la Conselleria de Sanidad y la comunicación con el promotor y Sanofi.

Cuarta.- Financiación

La Consellería de Sanidad pondrá a disposición los puntos de vacunación relacionados en el apartado 1.1.2. de la cláusula anterior, de modo que, en el marco general de realización de la campaña de vacunación de la gripe, el personal sanitario responsable de la vacunación en cada uno de esos puntos realice todas las actuaciones que sean necesarias de acuerdo con lo establecido en el protocolo del ensayo. Entre otras: información, recogida del consentimiento informado firmado, vacunación de las personas (pacientes) que participen en el ensayo y registro de los datos e información que proceda en su historia clínica.

La puesta a disposición de los puntos de vacunación para la realización del ensayo, así como el cumplimiento de los compromisos que asume la Consellería de Sanidad en el marco de este convenio no suponen un incremento del gasto, toda vez que las personas que participen en el ensayo tendrían derecho igualmente a vacunarse, ya que forman parte de los colectivos objeto diana de las campañas de vacunación de la gripe.

Por lo que se refiere a los compromisos que asume la Consellería para la realización del ensayo clínico GALFLU en general y, en particular, los indicados en la cláusula tercera del convenio, se ejecutan con medios propios, sin necesidad de incrementar el gasto, toda vez que se trata de compromisos que tienen encaje en las actividades de promoción de la investigación clínica propias de la Consellería y para la cual, con carácter ordinario, esta ya destina recursos materiales y humanos.

Asimismo, en el caso de que los objetivos que se persiguen con la realización del ensayo clínico GALFLU se alcancen y, en su caso, se demuestre la mayor eficacia de la vacuna sometida a ensayo, ello permitiría en un futuro obtener un balance altamente positivo en la ecuación coste/beneficio del Programa Gallego de Vacunación, así como la mejora de la calidad de vida de muchas personas que perteneciendo a la misma franja de edad de las que participan en el ensayo, se vacunen en un futuro.

Así, en el caso de que, finalmente, se demuestre la mayor eficacia de la vacuna sometida a ensayo, se reduciría el riesgo de hospitalización por gripe o neumonía y la hospitalización en el caso de personas con enfermedades cardio-respiratorias.

Quinta.- Plazo de vigencia y calendario de ejecución

El plazo de vigencia de este convenio va desde su firma hasta el 31 de diciembre de 2025.

En todo caso, el ensayo abarca las campañas de vacunación 2023/2024 y 2024/2025.

Con la finalidad de facilitar el control, seguimiento y cumplimiento de los hitos necesarios para la realización del ensayo las partes firmantes, en el plazo de un mes a contar desde el día siguiente a la firma de este convenio, elaborarán un calendario detallado en el que se recojan dichos hitos especificando, cuando proceda, los plazos parciales para su realización y la entidad o la persona o personas responsables de los mismos.

Dicho calendario se incorporará como un anexo al presente convenio, formando parte del mismo a efectos de su cumplimiento, sin perjuicio de que el mismo se pueda modificar justificadamente durante la vigencia del convenio. En todo caso, los ajustes y modificaciones que se realicen deberán quedar debidamente documentados.

Sexta.- Derechos de propiedad industrial o intelectual

1. En línea con lo establecido en la cláusula cuarta del convenio marco del que se deriva el presente convenio, por "*Derechos de Propiedad Industrial e Intelectual*" se entiende:

a) patentes, modelos de utilidad, certificados complementarios de protección, invenciones, diseños, derechos de autor y derechos conexos, derechos sobre bases de datos, marcas, nombres comerciales, denominaciones sociales y el derecho a solicitar su registro;

b) derechos sobre nombres de dominio;

c) Know-How;

d) solicitudes y renovaciones en relación con cualquiera de los anteriores derechos;

e) cualquier otro derecho de efecto equivalente en cualquier país del mundo;

f) licencias o derechos contractuales sobre cualquiera de los anteriores derechos;

2. El régimen de participación en la titularidad de los derechos de propiedad intelectual e industrial, así como de explotación, que surjan como consecuencia de los resultados científicos derivados de la actividad investigadora regulada en el marco de este convenio, será el establecido en el contrato de ensayo clínico.

Séptima.- Confidencialidad

1. A efectos de este convenio, se entiende por "*Información Confidencial*" la información que, con independencia de su soporte, físico o digital o de otro modo, tenga ese carácter (conste o no indicado en la misma o se desprenda de su naturaleza) en la medida en que:

a) sea secreta en el sentido de que no sea, como cuerpo o en la configuración y reunión precisas de sus componentes, generalmente conocida ni fácilmente accesible para personas introducidas en los círculos en que normalmente se utiliza el tipo de información en cuestión;

b) tenga un valor comercial por ser secreta; y

c) haya sido objeto de medidas razonables, en las circunstancias, para mantenerla secreta, tomadas por la persona que legítimamente la controla.

La información podrá comprender, de forma no exhaustiva, datos técnicos e informes, invenciones, software o mecanismos técnicos; dibujos técnicos y diseño; algoritmos, fórmulas matemáticas; ideas publicitarias; promociones, métodos de negocio; conocimientos y secretos comerciales; ejemplos, muestras y demostraciones; resultados de investigaciones; planes de negocios; datos financieros; datos comerciales; información relativa a negociaciones con terceras partes, documentos escritos, listados de clientes, grabaciones audiovisuales, u otro tipo de soporte técnico, etc. que sea generada durante y en relación con el desarrollo de este Convenio o con ocasión del mismo o proporcionada por cada una de las partes para su buen cumplimiento.

No se entenderá por información confidencial, ni recibirá tal tratamiento, aquella información que sea de público conocimiento en el momento de la firma del presente convenio y que así pueda ser demostrado mediante la consulta de archivos escritos, o que, después del mismo, alcance dicho carácter siempre y cuando la divulgación no se derive del incumplimiento por las Partes de las obligaciones del presente convenio.

2. Las partes firmantes se comprometen a:

a) tratar de forma reservada la información confidencial.

b) no divulgar la información confidencial a terceros salvo acuerdo expreso de las partes, o salvo imposición legal o resolución judicial firme.

c) no utilizar la información confidencial para fines no derivados del presente Convenio o de su desarrollo.

d) adoptar las precauciones razonables para proteger físicamente la integridad y confidencialidad de la información confidencial.

3. En el supuesto de terminación del convenio, las partes firmantes deben restituirse recíprocamente toda la documentación que hubiesen recibido en virtud del mismo con el carácter de confidencial, con arreglo a lo establecido en la cláusula quinta del convenio marco del que se deriva el presente convenio.

Así mismo, a la terminación del convenio, ninguna de las partes podrá divulgar ni utilizar comercialmente ni de cualquier otro modo la información proporcionada a título individual por cada una de ellas como parte integrante de la información confidencial a la que se ha tenido acceso.

No obstante la Consellería de Sanidad, por sí misma o a través de la Dirección General de Salud Pública, y el Servicio Gallego de Salud, se reservan la capacidad de guardar los registros derivados de la realización del ensayo clínico y ampliarlos más allá de lo establecido en él para llevar a cabo las acciones asistenciales y de salud pública que resulten necesarias para el cumplimiento de sus fines.

Octava.- Protección de datos

En relación con el tratamiento de los datos de carácter personal, las partes, en el desarrollo de sus correspondientes actividades derivadas del presente convenio, atenderán las disposiciones de obligado cumplimiento establecidas en la Ley Orgánica 3/2018, de 5 de diciembre, de Protección de datos personales y garantía de los derechos digitales así como en el Reglamento (UE) 2016/679 del Parlamento Europeo y del Consejo, de 27 de abril de 2016, relativo a la protección de las personas físicas en lo que respecta al tratamiento de datos personales y a la libre circulación de estos datos y por el que se deroga la Directiva 95/46/CE (Reglamento general de protección de datos).

De acuerdo con lo anterior, el promotor del ensayo actuará como responsable de tratamiento de los datos relativos a dicho ensayo, mientras que la Consellería de Sanidad actuará como responsable de tratamiento de Historia Clínica.

En cumplimiento de la mencionada normativa, las partes se comprometen a atender los derechos de los interesados, la obtención del consentimiento cuando sea exigible, y demás requerimientos exigidos por la normativa de protección de datos.

A estos efectos la comunicación con los interesados se realizará a través de los delegados de protección de datos de las entidades conveniantes.

Las partes están obligadas a guardar el secreto profesional respecto de los datos de carácter personal que trate en cumplimiento del convenio, obligación que subsistirá aún cuando cuando finalice la vigencia del presente convenio.

Novena.- Comisión de seguimiento

Se constituirá una comisión de seguimiento que interprete y asegure el buen fin y cumplimento del objecto del convenio y que resuelva las controversias surgidas como consecuencia de su ejecución.

La comisión estará formada por:

1. Dos personas de la Consellería de Sanidad, una de las cuales será la titular da Dirección General de Salud Pública (o persona en quién delegue), quién además la presidirá y tendrá voto de calidad en caso de empate.

2. Dos personas por parte de la FIDIS, una de las cuales será la persona titular de la presidencia (o persona en quien delegue).

Asimismo, a las reuniones de la comisión de seguimiento podrán asistir, cuando se considere necesario otras personas, con voz pero sin voto.

El régimen de funcionamiento de esta comisión será el establecido en la Sección 3ª del Capítulo II de la Ley 40/2015, de 1 de octubre, de Régimen Jurídico do Sector Público. Será función de esta comisión garantizar el cumplimento de los objetivos y obligaciones del convenio y promover la producción científica derivada de los resultados del mismo.

Son funciones de esta comisión de seguimiento:

a) El seguimiento del desarrollo y aplicación del presente convenio y de las actividades realizadas, así como la adopción de decisiones sobre los mismos.

b) La coordinación de las acciones de apoyo a la protección, valorización y transferencia, y el desarrollo de los medios adecuados para su implementación, de ser preciso.

c) La resolución de aquellas dudas que hayan podido surgir en el cumplimiento, ejecución o interpretación de este convenio.

d) La propuesta de modificación de las cláusulas contenidas en el presente convenio y, en su caso, de la documentación anexa al mismo, excepto la documentación propia del expediente del ensayo.

Décima.- Naturaleza y régimen jurídico

El presente convenio tiene naturaleza administrativa, tratándose, según lo previsto en el artículo 6.1 de la Ley 9/2017, de 8 de noviembre, de Contratos do Sector Público, por la que se traspone al ordenamiento jurídico español las Directivas do Parlamento Europeo y del Consejo 2014/23/UE y 2014/24/UE, de 26 de febrero de 2014, de un negocio jurídico excluido del ámbito de aplicación de aquella.

De conformidad con el artículo 4 de esa misma norma, este convenio se regirá por sus normas especiales, aplicándose los principios de esta ley para resolver las dudas y lagunas que pudiesen presentarse.

Las partes se comprometen a resolver de manera amigable cualquier desacuerdo que pudiera surgir en el desarrollo del presente convenio. Si el acuerdo no fuese posible, las partes se comprometen a someterse a mediación, antes de iniciar cualquier reclamación, ante la jurisdicción competente en la materia. Las cuestiones litigiosas que puedan surgir en la interpretación o en el incumplimiento de las obligaciones que se deriven del presente convenio, y que no puedan ser dirimidas por la comisión de seguimiento creada para tal efecto, quedarán sometidas a la jurisdicción contencioso administrativa, de conformidad con la Ley 29/1998, do 13 de julio, reguladora de dicha jurisdicción.

Décimo primera.- Modificación

La modificación del contenido del convenio requerirá acuerdo unánime de los firmantes.

Décimo segunda.- Causas de resolución

El convenio se extinguirá por el cumplimiento de las actuaciones que constituyen su objeto o por incurrir en causa de resolución. A estos efectos, son causas de resolución:

a) El transcurso del plazo de vigencia del convenio sin haberse acordado la prórroga del mismo.

b) El acuerdo unánime de todas las partes firmantes.

c) El incumplimiento de las obligaciones y compromisos asumidos por parte de alguna de las partes.

En este caso, cualquiera de las partes podrá notificar a la parte incumplidora un requerimiento para que cumpla en un determinado plazo con las obligaciones o compromisos que se consideran incumplidos. Este requerimiento será comunicado al responsable del mecanismo de seguimiento, vigilancia y control de la ejecución del convenio y a las demás partes firmantes.

Si trascurrido el plazo indicado en el requerimiento persistiera el incumplimiento, la parte que lo dirigió notificará a las partes firmantes la concurrencia de la causa de resolución y se entenderá resuelto el convenio.

d) Por decisión judicial declaratoria de la nulidad del convenio.

e) Por cualquier otra causa distinta de las anteriores prevista en el convenio o en otras

leyes.

Sin perjuicio de lo anterior, las partes podrán interrumpir en cualquier momento el ensayo amparado por el presente convenio. También estará facultada para interrumpir o dar por terminado el presente convenio en el caso de que el desarrollo del ensayo se considere insatisfactorio o se considere innecesaria su continuación por cualquier otro motivo.

Cualquiera de las partes puede terminar o desistir del convenio en cualquier momento sin necesidad de alegar causa alguna, notificándoselo a la otra parte por escrito con un preaviso no inferior a treinta días. La terminación no libera a las partes de las obligaciones adquiridas a la fecha de la terminación ni de las obligaciones que de acuerdo con sus términos persistan tras la terminación, incluyendo la confidencialidad pertinente, el mantenimiento de archivos, el cumplimiento con las normas administrativas, las relativas a la propiedad industrial e intelectual, etc.

Décimo tercera.- Publicación

Las partes acuerdan que los resultados del ensayo puedan publicarse por cualquiera de ellas, previa autorización expresa y por escrito de la otra sobre su divulgación y sobre el contenido de dicha publicación. La publicación hará expresa referencia a la colaboración y cooperación entre las partes fruto del convenio.

Décimo cuarta.- Notificaciones

Todas las notificaciones de una parte a otra se realizarán por escrito y se dirigirán a la otra parte a la dirección de correo postal o de correo electrónico expresados en este convenio. Para el caso de que, con posterioridad, se modifique la dirección de correo postal o de correo electrónico, la otra parte será informada de ello por escrito.

1. Las comunicaciones y notificaciones a la Consellería de Sanidad, se dirigirán a la Dirección General de Salud Pública, Edificio administrativo San Lázaro, s/n, 15703.

Santiago de Compostela. Correo-e: saude.publica@sergas.es

2. Las comunicaciones y notificaciones a FIDIS, de carácter administrativo, se dirigirán a: Isabel Lista García, FIDIS (Edificio D, Planta 1ª), Hospital Clínico Universitario de Santiago, Travesía da Choupana sn, 15706, Santiago de Compostela (A Coruña). Correo-e: isabel.lista.garcia@sergas.es

3. Las comunicaciones y notificaciones a FIDIS, de carácter científico, se dirigirán a:

Dr. D. Federico Martinón Torres, Pediatría, Hospital Clínico Universitario de Santiago, Travesía da Choupana sn, 15706, Santiago de Compostela (A Coruña). Correo-e: federico.martinon.torres@sergas.es, en calidad de coordinador del Grupo de Investigación en vacunas e infecciones (GENVIP), C020, del Instituto de Investigación Sanitaria de Santiago de Compostela (IDIS).

Todas las notificaciones serán efectivas a partir de su recepción.

Décimo quinta.- Registro de convenios, transparencia y buen gobierno

La firma de este convenio lleva implícito el consentimiento expreso de las personas intervinientes para que la Administración pública autonómica gallega pueda hacer públicos los datos de carácter personal y cualesquiera otras especificaciones que figuren en él, de acuerdo con lo dispuesto en la Ley 19/2013, de 9 de diciembre, de transparencia, acceso a la información pública y buen gobierno, y en la Ley gallega 1/2016, de 18 de enero, de transparencia y buen gobierno.

El presente convenio será objeto de inscripción en el Registro de Convenios de la Xunta de Galicia, en los términos previstos en el Decreto 126/2006, de 20 de junio, por el que se regula el Registro de Convenios de la Xunta de Galicia.

Y, en prueba de conformidad y para la debida constancia de todo lo convenido, ambas partes firman electrónicamente el presente documento.

Por la Consellería de Sanidad y el Servicio Gallego de Salud	**Por la Fundación Instituto de Investigación Sanitaria de Santiago de Compostela,**
Fdo.: Julio García Comesaña	Fdo.: Isabel Lista García

ANEXO

Protocolo del ensayo

Pragmatic Randomized Trial to Evaluate the Effectiveness of High-Dose Quadrivalent Influenza Vaccine vs. Standard-Dose Quadrivalent Influenza Vaccine in adults aged 65 to 79 years in Galicia, Spain

(GALFLU)

Study Protocol

Version 1.0
05 June 2023

EU CT number: 2023-506977-36-00

Sponsor:

Prof. Dr. Federico Martinón Torres, MD, PhD.

Hospital Clínico Universitario de Santiago de Compostela

Department of Pediatrics

Travesía da Choupana s/n

15706 Santiago de Compostela (Spain)

Principal Investigator:

Prof. Dr. Federico Martinón Torres, MD, PhD.

Hospital Clínico Universitario de Santiago de Compostela

Department of Pediatrics

Travesía da Choupana s/n

15706 Santiago de Compostela (Spain)

Investigator:

Susana Mirás Carballal

Dirección Xeral de Saúde Pública. Consellería de Sanidade. Xunta de Galicia

Edificio Administrativo de San Lázaro

15781 Santiago de Compostela (Spain)

Trial sites and protocol signatures

Hospital Clínico Universitario de Santiago de Compostela

Sponsor-investigator site

Department of Pediatrics

Travesía da Choupana s/n

15706 Santiago de Compostela (Spain)

Principal Investigator: Dr. Federico Martinón Torres, MD, PhD.

Signature:

Firmado digitalmente por MARTINON TORRES FEDERICO - 34987689C
Fecha: 2023.07.12 19:34:02 +02'00'

Dirección Xeral de Saúde Pública. Consellería de Sanidade. Xunta de Galicia

Vaccination sites

Edificio Administrativo de San Lázaro

15781 Santiago de Compostela (Spain)

Investigator: Susana Mirás Carballal

Signature:

MIRAS CARBALLAL SUSANA - 45849838M

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1. Introduction

1.1. Background

Influenza disease is a contagious, acute viral respiratory illness that may affect all age groups with presentations ranging from mild upper respiratory symptoms to severe cases resulting in hospitalization and/or death. In the northern and southern hemispheres, influenza causes seasonal epidemics of disease almost every winter. In tropical regions, influenza circulates continuously throughout the year, causing outbreaks more irregularly[1]. Using data between 1999 and 2015 on seasonal influenza, global estimates of influenza-associated mortality and morbidity indicate that influenza causes between 290,000 and 650,000 respiratory deaths which is equivalent to 4·0–8·8 deaths per 100 000 individuals, and approximately five million hospitalizations for lower respiratory tract infection annually[2,3]. The elderly (aged 65 and above) and individuals with chronic healthcare conditions such as heart disease, lung disease, or diabetes display a heightened risk of influenza complications compared to younger healthy adults[4,5]. Vaccination is the most effective means of reducing the incidence of influenza and influenza-related morbidity and mortality[6]. Seasonal vaccination of persons aged 65+ and other high risk groups is strongly recommended by the European Centre for Disease Control and numerous national governmental immunization guidelines; in the United States, the Centers for Disease Control and Prevention additionally recommends vaccination for all persons aged ≥6 months without contraindications[4,5].

Previous studies have shown that antibody response and protection elicited by the standard formulation influenza vaccine are reduced for individuals aged 65 years or older as compared to younger adults[7,8]. A high-dose (HD) influenza vaccine formulation (Fluzone® High-Dose), containing 60 µg of antigen from each influenza strain included in the vaccine, has been shown in a US randomized clinical trial (RCT) to reduce the incidence of influenza by 24.2% with no increase in serious adverse events compared to standard-dose (SD) vaccine formulations in persons aged 65 or more[9]. The lower bound of the 95% confidence interval (CI) was 9.7% satisfying the prespecified superiority criterion. A subsequent analysis

showed higher efficacy for HD vs. SD in preventing adjudicated serious cardio-respiratory events (defined as pneumonia, asthma/chronic obstructive pulmonary disease (COPD)/bronchial events, influenza, coronary artery events, congestive heart failure, cerebrovascular events, and other respiratory events) with a relative vaccine effectiveness (rVE) of 17.7% (95% CI: 6.6%–27.4%)[10].

The relative vaccine efficacy/effectiveness of HD vs. SD has been consistently confirmed over multiple seasons (against matched/mismatched strains), against multiple endpoints, and across different study designs – as shown in a recent meta-analysis from Lee et al., 2021[11]. In this paper, 15 publications were meta-analyzed after screening 1,293 studies, providing data on 10 consecutive influenza seasons and over 22 million individuals receiving HD influenza vaccines in randomized and observational settings. Across all influenza seasons, HD demonstrated improved protection against influenza-like illness compared to SD (rVE = 15.9%, 95% CI: 4.1%–26.3%). HD was also more effective at preventing hospital admissions from any cause (rVE = 8.4%, 95% CI: 5.7%–11.0%) as well as influenza (rVE = 11.7%, 95% CI: 7.0–16.1%), pneumonia (rVE = 27.3%, 95% CI: 15.3%–37.6%), combined pneumonia/influenza (rVE = 13.4%, 95% CI: 7.3%–19.2%), and cardiorespiratory events (rVE = 17.9%, 95% CI: 15.0%–20.8%). Reductions in mortality due to pneumonia/influenza (rVE = 39.9%, 95% CI: 18.6–55.6%) and cardiorespiratory causes (rVE = 27.7%, 95% CI: 13.2%–32.0%) were also observed. Similar pooled rVEs were observed in both matched and mismatched seasons and in seasons where A/H3N2 or A/H1N1 strains were predominantly circulating. A recent cluster-randomized trial also found that the HD vaccine reduced respiratory-related hospital admissions in nursing home residents aged 65+ when compared to SD vaccines[12].

A quadrivalent formulation of the HD influenza vaccine (QIV-HD; Efluelda®) was licensed for use in persons aged 65+ in Europe in April 2020. In the Galician 2021/2022 influenza season, a trivalent

adjuvanted vaccine was offered to citizens aged 65 and above and QIV-HD vaccine was offered to citizens aged 60 and above who were nursing home residents only. In the 2022/2023 influenza season, the Galician government vaccination program was expanded to offer QIV-HD vaccine to citizens aged 85 years and above and citizens aged 60 and above who were nursing home residents, while citizens aged 65-84 years were offered SD vaccines despite evidence indicating that the HD vaccine could reduce morbidity and improve clinical outcomes in this population group. However, to the best of our knowledge, beyond the recent feasibility study in Denmark (DANFLU-1) which looked at clinically relevant endpoints in an exploratory manner[13], no individually randomized studies have assessed the effect of HD vs SD influenza vaccine on the incidence of hospitalizations for influenza or pneumonia and mortality. Influenza vaccine acceptance in the elderly in Galicia is among the highest in the EU and has been steadily increasing from 2012 to 2022 with 50.93% and 76% coverage respectively[14]. Currently in Galicia, QIV-HD is recommended from 80 years of age and above. There would be a significant public health interest in quantifying the potential benefit of QIV-HD vs SD quadrivalent influenza vaccine (QIV-SD) with respect to clinically important and impactful outcomes such as hospitalization for influenza or pneumonia in the 65-79 years age group. Such information would be crucial in performing cost-effectiveness analyses to guide future vaccination policies.

RCTs serve as the gold standard for decision-making and are required for the registration of any new vaccines[15]. However, their results can have limited generalizability due to their highly controlled nature and restrictive inclusion/exclusion criteria. Building upon the evidence generated by these traditional RCTs, studies combining randomization within vaccination programs with outcome follow up via nationwide healthcare databases provide the opportunity to combine the gold standard of individual randomization – thereby providing unbiased results from which causal conclusions can be inferred – with representative real-world patient populations and pragmatic data collection[16]. With this approach,

rigorous randomization of treatment allocation is integrated with existing data-collection platforms which may be used to collect baseline and follow-up information, greatly reducing complexity and costs. In Galicia, regional administrative registries enable effective collection of such information for all persons residing in Galicia. This is highly desirable in studies comparing one vaccine to another since these studies involve the estimation of relatively small effect sizes as compared to placebo-controlled studies, requiring large sample sizes.

1.2. Purpose

This pragmatic randomized trial is designed to evaluate the relative vaccine effectiveness of QIV-HD vs. QIV-SD in reducing the risk of hospitalization for influenza or pneumonia in adults 65-79 years of age in Galicia during 2023/2024 and 2024/2025 seasons.

2. Study objectives

The registry-based endpoints corresponding to the following study objectives are further specified in section 7.3. The study is designed to achieve at least 80% statistical power for the primary objective, hospitalization for influenza or pneumonia [composite endpoint].

2.1. Primary objective

The primary objective of the study is to evaluate the relative vaccine effectiveness of QIV-HD vs. QIV-SD in reducing the risk of hospitalization for influenza or pneumonia [composite endpoint] in adults aged 65 to 79 years.

2.2. Secondary objective

The secondary objectives of the study are to evaluate the relative vaccine effectiveness of QIV-HD vs. QIV-SD in reducing the risk of the following endpoints in adults aged 65 to 79 years:

1. Hospitalization for any cardio-respiratory disease [composite endpoint]
2. All-cause hospitalization
3. All-cause mortality
4. Hospitalization for influenza
5. Hospitalization for pneumonia

2.3. Exploratory objectives

The exploratory objectives of the study are to evaluate the relative vaccine effectiveness of QIV-HD vs. QIV-SD in reducing the risk of the following endpoints in adults aged 65 to 79 years:

1. Hospitalization for influenza or pneumonia [composite endpoint] (alternate definition, see section 7.3)
2. Hospitalization for pneumonia (alternate outcome definition, see section 7.3)
3. Hospitalization for influenza (alternate outcome definition, see section 7.3)
4. Hospitalization for any respiratory disease
5. Hospitalization for any cardiovascular disease
6. Hospitalization for myocardial infarction
7. Hospitalization for heart failure
8. Hospitalization for atrial fibrillation
9. Hospitalization for stroke
10. Major adverse cardiovascular events (MACE) defined as a composite of hospitalization for acute myocardial infarction, hospitalization for stroke, and cardiovascular death

11. MACE defined as a composite of hospitalization for acute myocardial infarction, hospitalization for stroke, hospitalization for heart failure, and cardiovascular death (alternate MACE definition #1)
12. MACE defined as a composite of hospitalization for acute myocardial infarction, hospitalization for stroke, and all-cause death (alternate MACE definition #2)
13. Hospitalization requiring mechanical ventilation
14. Laboratory-confirmed influenza
15. Laboratory-confirmed pneumococcal pneumonia
16. Laboratory-confirmed COVID-19
17. Cardio-respiratory mortality
18. Respiratory mortality
19. Cardiovascular mortality
20. In-hospital mortality for any cause

2.4. Healthcare resource consumption objective

Healthcare resource consumption and associated costs will be evaluated according to the QIV-HD vs QIV-SD arms including, but not limited to:

1. Any hospital contacts
2. Hospitalizations requiring mechanical ventilation
3. Duration of hospitalization stays for:
    - Influenza or pneumonia
    - Any cardio-respiratory disease
    - Influenza
    - Pneumonia

4. Primary care visits
5. Nursing home admission (following any all-cause hospitalization)
6. Anti-infective use

3. Study organization

The trial will be sponsored by Dr. Federico Martinón Torres who will also act as the principal investigator. The trial will be supported by the Galician Health Service through the General Public Health Directorate and the Regional Vaccination Program of Galicia.

The General Public Health Directorate through the Regional Vaccination Program of Galicia has a well-established network of vaccination sites where seasonal flu vaccine is usually administered. This vaccination sites depend on the General Public Health Directorate and will be coordinated within the clinical trial by Susana Mirás Carballal, Head of the Disease Control Service and investigator of the trial. Roles and responsibilities will be properly delegated by the principal investigator.

Study procedures will be performed in the vaccination sites established within the Influenza Regional Vaccination Program of Galicia. A research team will be formed of medical doctors, nurses, and other medical professionals deemed capable of performing trial duties to whom Dr. Federico Martinón Torres may delegate trial-related procedures.

4. Experimental plan

4.1. Study design

The study is a pragmatic, registry-based, open-label, active-controlled, individually randomized trial using the infrastructure of the Regional Vaccination Program of Galicia for patient recruitment, inclusion, randomization, and vaccine administration and the Galician health registries for data collection including baseline information, follow-up data and safety monitoring.

Recruitment will be performed as a collaboration between the sponsor-principal investigator and the Regional Vaccination Program of Galicia allowing for a region-wide recruitment using the Galician administrative registries, text message system and social media.

Participants will have the opportunity of receiving all the information for the trial prior to the vaccination appointment. Informed consent will be obtained during the vaccination appointment by the study team prior to their vaccine administration. The participation in the study is voluntary, and only individuals who accept signing the informed consent will be recruited. Participants may withdraw from the study at any point.

The study aims to randomize at least 114.011 participants over 2 influenza seasons (2023/2024 and 2024/2025) with approximately 57,000 participants per season (pending any further potential sample size adjustments following interim analysis). In each season, participants will be individually randomized 1:1 to receive either QIV-HD or QIV-SD. Participants, who are randomized in the first season and wish to participate again in the second season, will be re-randomized.

The study will comply with the principles of the Declaration of Helsinki and undergo monitoring according to the International Conference on Harmonization guidelines for Good Clinical Practice.

4.2. Study period

The study will be conducted across 2 influenza seasons (2023/2024 and 2024/2025). Participant enrollment is expected to run from October through December within each season. In each season, participants will be followed for the occurrence of endpoint events from 14 days after vaccination until May 31 the following year (extended until August 31 for additional sensitivity analyses). A prespecified interim analysis may be performed immediately after completion of follow-up for clinical endpoints for the 2023-2024 season (follow-up completed on May 31, 2023) by the sponsor, pending the influenza

circulation threshold as described in section 9.3. The study may stop for superior efficacy if the primary objective is achieved according to section 9.4 of the protocol.

The end of the trial will be defined as the end of the final period of extended follow-up (August 31) following the final season.

4.3. Data collection

The trial involves minimal data collection by site personnel. Once the informed consent is obtained, trained vaccine site personnel will confirm that the participant exhibits no contraindications towards vaccination before randomizing and administering the vaccine. Participants will be assigned a unique subject code and will be randomized using electronic randomization lists.

All data collection will be done using the Galician health registries. The sponsor- principal investigator will ensure access to the relevant registries upon agreement with the General Directorate of Public Health prior to the enrollment of any participant.

Galician health registries contain information on all in- and out-patient visits, prescriptions and diagnostic tests performed in the Galicia public health system and vaccinations as it is detailed below.

The following Galician health registries will be used for the data collection within the clinical trial:

- CMBD (Conjunto Mínimo Básico de Datos): data regarding hospitalization – e.g. ICD 10 codes (discharge diagnosis), in-hospital mortality, and length of hospitalization, among others.
- Tarxeta sanitaria: personal identification data such as age, sex and address.
- Rexistro galego de mortalidade: date and cause of death
- SIHGA (Sistema información hospitalaria de Galicia). all cause hospitalization, hospitalization contacts (date of admission, date of discharge, in-hospital mortality…)
- Etiquetas clínicas: morbidity related with the most prevalent chronic diseases
- Rexistro Atención primaria: primary care visits

- REVACU (rexistro de vacinas): vaccine registries
- Rexistro de dispensación de farmacia: Anatomical Therapeutic Chemical (ATC) codes
- Microbioloxia: laboratory confirmed respiratory infections (e.g. influenza, COVID 19, pneumococcus…)

Trial participants will allow access to their medical records when signing the informed consent form. Medical records will be used for collecting additional information about potential safety events experienced by trial participants.

4.4. Data security and anonymization

Once informed consent is signed, data collected from each subject will be identified with a unique code number. The link between personal data and the subject code will be recorded in a subject identification code list which access will be restricted to the research team. The confidentiality of the data of the subjects participating in the trial will be guaranteed, ensuring compliance with Organic Law 3/2018, of December 5, Protection of personal data and guarantee of digital rights as well as General Data Protection Regulation (GDPR). Any patient data transferred from the site will be fully pseudonymized and handled according to appropriate regulations.

5. Study population

5.1. Participant recruitment and informed consent

Participants will be invited to take part in the trial through different channels:

- Through the applications of the General Public Health Directorate (text message information about the trial will be sent to the potential participants).

- The General Public Health Directorate will advertise the trial through their website, social media and other means of communication such as announcement posts.

It is expected that around 400,000 persons will receive information about the trial. Detailed information of the trial will be available in the webpage of the Influenza Regional Vaccination Program of Galicia where the informed consent form will be available and ready to download. After this preliminary information, a contact phone number will be provided to answer inquiries and provide further information to the potential participants. Full information about the trial will be provided during the informed consent procedure during the vaccination appointment and prior to any data collection or vaccine administration.

During the vaccination visit, the patient information sheet and informed consent form will be provided to the individuals potentially interested in participating in the trial. Oral information will be provided, enough time to read the patient information sheet will be given and all questions will be answered by a trained medical professional of the research team before the participant takes the decision to enroll in the study. Two copies of the informed consent form will be signed, one of which will be given to the participant once they have agreed to participate.

In case of refusal to participate in the trial during the informed consent procedure, QIV-SD vaccine will be offered as per usual practice. The participation in the study is voluntary, and only individuals who accept signing the informed consent will be recruited. Participants may withdraw from the study at any point and only data collected to the time of the withdrawn will be analyzed.

5.2. Inclusion criteria

1. Age 65-79 years residing in the community (only individuals who are not eligible to receive QIV-HD as part of the standard of care)

2. Informed consent form has been signed and dated

Whether a potential participant fulfills the above inclusion criteria will be judged by the trained medical professional who obtains informed consent for trial participation.

5.3. Exclusion criteria

There are no specific exclusion criteria for this study; however, at time of writing those residing in nursing homes should receive QIV_HD as standard of care, so would be ineligible for this study.

Vaccines assessed in this study will be administered in a routine clinical practice setting as part of the Regional Vaccination Program of Galicia and will be administered in accordance with the indication specified in the marketing approval – this may additionally include co-administration with COVID-19 vaccines/boosters as per local guidance/recommendations.

Whether contraindications to influenza vaccination are present, they will be determined as per routine practice by the trained medical professional at the vaccination visit.

6. Treatment

6.1. Background of the investigational treatment

The QIV-HD (Efluelda®) vaccine received marketing approval in European Union for use in persons aged 65 and older in April 2020 with an age extension from 60 years of age and older in March 2021. Please see the introduction section of this protocol and the enclosed product summary for further information. The vaccine is manufactured and provided by Sanofi.

6.2. Identity of the investigational treatment

The QIV-HD is a split virion inactivated quadrivalent influenza vaccine (60 micrograms of HA/strain/dose) and will contain the virus strains recommended by the World Health Organization for

egg-based quadrivalent influenza vaccines in the upcoming 2023/2024 and 2024/2025 northern hemisphere influenza seasons.

Each pre-filled syringe, (type I glass) equipped with a plunger stopper (bromobutyl rubber) and a tip cap, contains 240 micrograms total HA antigen (60 micrograms from each strain) per 0.7mL dose provided in sterile suspension for intramuscular injection.

In addition, each dose contains the following excipients: Buffered saline solution Q.S. to appropriate volume and up to no more than 350 micrograms of octoxinol-9.

Each dose may also contain residual traces of egg components such as ovalbumin, formaldehyde and octoxynol-9. Each dose will contain no more than 1 microgram of ovalbumin.

Please refer to the product summary for further details.

6.3. Preparation and administration of investigational treatment

For pragmatic reasons, the QIV-HD investigational treatment will be administered by a trained medical professional according to the routine clinical practice procedures normally used when administering influenza vaccines as part of the Influenza Regional Vaccination Program of Galicia. The vaccine is provided in a pre-filled single dose syringe (type I glass). The needle will be provided separately at the vaccination sites.

The routine procedure includes observation after vaccine administration. Each vaccination site will maintain proper medical equipment and emergency medications, including epinephrine, for administration in case a participant develops an anaphylactic or immediate allergic reaction.

6.4. Identity and administration of the control treatment

In this study, the comparator treatment will be a QIV-SD vaccine administered as part of the standard Influenza Regional Vaccination Program of Galicia, namely, Influvac tetra® for the 2023-2024 season.

These vaccines will contain 15 micrograms of each included influenza strain. The influenza strain composition will be identical to the strains included in the QIV-HD vaccine and match the World Health Organization recommendations for the 2023/2024 and 2024/2025 northern hemisphere seasons. For pragmatic reasons, this trial will not impose any absolute restrictions on the QIV-SD comparator vaccine and will include any SD-QIV vaccine decided upon by the government.

The administration of the QIV-SD comparator vaccine will follow the same routine clinical procedures used for the administration of the QIV-HD vaccine.

6.5. Additional study treatment

No additional study treatment will be provided for this trial.

6.6. Labelling and packaging

The QIV-HD vaccine (Efluelda®) will be provided by Sanofi and will be provided in a Spanish commercial packaging. The QIV-SD comparator treatment will be packaged according to national guidelines for marketed pharmaceuticals, since these will be comprised of the vaccines procured by the Influenza Regional Vaccination Program of Galicia. Since neither the QIV-HD or the QIV-SD comparator vaccine will be handed over unused to any trial participant, the products will not be relabeled with investigational labeling.

6.7. Product shipment and storage

The QIV-HD vaccines (and any additional QIV-SD doses) will be shipped from Sanofi to the General Public Health Directorate, and then shipped to the vaccination sites according to routine vaccine shipment procedures implemented through the Influenza Regional Vaccination Program of Galicia. Vaccine will be shipped and stored at 2-8 degree Celsius, cold chain maintenance will be ensured during all the

process. Monitoring of drug accountability, drug storage, temperature logging, distribution of vaccines to vaccination sites and handling of the vaccines at the vaccination sites will all be done according to the standard procedures.

Any QIV-HD doses not used in the study will be destroyed by the sponsor.

6.8. Blinding

The trial is open-label. Neither investigators, medical professionals nor trial participants will be blinded to treatment allocation. Although the trial is open-label, negligible bias is expected due to the nature of hospitalization endpoints based on registry data.

6.9. Randomization and treatment allocation

Trial participants will be randomized 1:1 to receive a QIV-HD or QIV-SD vaccine. Randomization will be performed centrally using a computer-generated block randomization scheme.

A participant randomized to QIV-HD or QIV-SD arm in the first influenza season could be re-randomized to either treatments in the following season.

6.10. Study termination

The sponsor- principal investigator reserves the right to terminate the study at any time for any reason at the sole discretion of the sponsor-investigator. Reasons for early study termination may include but are not limited to:

- Information on the study intervention leads to doubt as to the benefit/risk ratio
- Required sample size is reached earlier than expected
- Loss of funding

- After the interim analysis performed immediately after completion of follow-up for clinical endpoints for the 2023-2024 season for reasons stated in section 9.4.

If the study is prematurely terminated or suspended, the sponsor-investigator shall promptly inform participants, investigators, and relevant authorities of the reason for termination or suspension, as specified by the applicable regulatory requirements.

7. Visit schedule and assessments

7.1. Visits

This trial includes only a single visit. Trial participants will be vaccinated at the vaccination sites within the Influenza Regional Vaccination Program of Galicia. No further visits are scheduled in this trial.

7.2. Baseline information

Information on baseline characteristics will be collected from regional administrative registries for all trial participants. The following registry-based definitions will be used for the assessment of baseline characteristics:

Prespecified Definitions for Baseline Conditions

Condition	ICD-10/ATC codes	Diagnosis type	Inpatient/outpatient/ minimum required length of stay/other criteria	Timeframe
No. of hospitalizations in last 12 months	Any	Any	Inpatient, at least 1 night	≤12 months prior to randomization
No. of hospitalizations in last 10 years	Any	Any	Inpatient, at least 1 night	≤10 years prior to randomization
No. of hospital contacts in last 12 months	Any	Any	Inpatient, at least 1 night	≤12 months prior to randomization

No. of hospital contacts in last 10 years	Any	Any	Inpatient, at least 1 night	≤10 years prior to randomization
No. of primary care contacts in last 12 months	Any	Any	-	≤10 years prior to randomization
No. of primary care contacts in last 10 years	Any	Any	-	≤10 years prior to randomization
Chronic obstructive pulmonary disease	J42-J44	A or B	Any	≤10 years prior to randomization
Asthma	J45	A or B	Any	≤10 years prior to randomization
Chronic lung disease	A15-A16, D860, E84, J42-J47, J84, Z942	A or B	Any	≤10 years prior to randomization
Diabetes (ICD-10)	E10-E14	A or B	Any	≤10 years prior to randomization
Diabetes (ATC)	A10	-	≥1 claimed prescription	≤180 days prior to randomization
Hypertension (ICD-10)	I10-I15	A or B	Any	≤10 years prior to randomization
Hypertension (ATC)	Diuretics: C03 β-blockers: C07 Calcium blockers: C08 Renin-angiotensin system inhibitors: C09	-	≥1 claimed prescription from ≥2 drug classes	≤180 days prior to randomization
Dyslipidemia (ATC)	C10	-	≥1 claimed prescription	≤180 days prior to randomization
Ischemic heart disease	I20-I25	A or B	Any	≤10 years prior to randomization
Myocardial infarction	I21	A or B	Any	≤10 years prior to randomization
Heart failure	I50	A or B	Any	≤10 years prior to randomization
Other cardiomyopathy	I42-I43	A or B	Any	≤10 years prior to randomization
Atrial fibrillation	I48	A or B	Any	≤10 years prior to randomization

Other arrhythmia	I44-I47, I49	A or B	Any	≤10 years prior to randomization
Valvular disease	I34-I37	A or B	Any	≤10 years prior to randomization
Pericarditis	I30-I31	A or B	Any	≤10 years prior to randomization
Endocarditis	I33, I38-I39	A or B	Any	≤10 years prior to randomization
Myocarditis	I40-I41	A or B	Any	≤10 years prior to randomization
Pulmonary heart disease	I26-I28	A or B	Any	≤10 years prior to randomization
Cerebrovascular disease	I60-I69	A or B	Any	≤10 years prior to randomization
Peripheral vascular disease	I70, I74	A or B	Any	≤10 years prior to randomization
Congenital heart disease	Q20-Q26	A or B	Any	≤10 years prior to randomization
Chronic cardiovascular disease	I20-I28, I34-I37, I42-I50, I60-I69, I70, I74, Q20-Q26	A or B	Any	≤10 years prior to randomization
Cancer	C00-C97 (not C44)	A or B	Any	≤10 years prior to randomization
Chronic kidney disease	E102, E112, E132, E142, I120, N02-N08, N11-N12, N14, N18-N19, N26, N158-N160, N162-N164, N168, M300, M313, M319, M321B, Q612-Q613, Q615, Q619, T858-T859, Z992	A or B	Any	≤10 years prior to randomization
Liver disease	B15-B19, K70-K77, C22, I982, Z944, D684C, Q618	A or B	Any	≤10 years prior to randomization
Immunodeficiency (ICD-10)	B20-B24, D80-D84, D89, O987,	A or B	Any	≤10 years prior to randomization

	Z21, Z940-Z944, Z948A			
Immunodeficiency (ATC)	H02AB, L04	-	≥1 claimed prescription	≤180 days prior to randomization
Neurological/ neuromuscular disease	F00-F03, G10-G14, G20-G23, G30-G32, G35-G37, G40-G41, G70-G73, G80-G83, G91-G95	A or B	Any	≤10 years prior to randomization
Dementia	F00-F03, G30, G311-G312,	A or B	Any	≤10 years prior to randomization
Rheumatic disease	M05-M06, M32-M34, M353	A or B	Any	≤10 years prior to randomization
Anemia	D50, D62, D64	A or B	Any	≤10 years prior to randomization
Presence of at least one chronic disease	At least one of the following: - Chronic lung disease - Diabetes - Chronic cardiovascular disease - Cancer - Chronic kidney disease - Immunodeficiency - Neurological/neuromuscular disease - Liver disease - Rheumatic disease	-	-	-

* A = primary discharge diagnosis; B = secondary discharge diagnosis

All baseline conditions are defined from ICD-10 codes except for diabetes, hypertension, dyslipidemia, and immunodeficiency, where ATC codes are also used. ICD, International Classification of Diseases; ATC, Anatomic Therapeutic Chemical.

Prespecified Definitions for Medication Use at Baseline

Medication	ATC codes	Number of prescriptions	Timeframe
Antithrombotics	B01	≥1 claimed prescription	≤180 days prior to randomization
Renin-angiotensin system inhibitor	C09	≥1 claimed prescription	≤180 days prior to randomization
Calcium blockers	C08	≥1 claimed prescription	≤180 days prior to randomization
Beta blockers	C07	≥1 claimed prescription	≤180 days prior to randomization
Diuretics	C03	≥1 claimed prescription	≤180 days prior to randomization
Aspirin	B01AC06	≥1 claimed prescription	≤180 days prior to randomization
Statins	C10AA	≥1 claimed prescription	≤180 days prior to randomization
Inhaled beta-2 agonists	R03A	≥1 claimed prescription	≤180 days prior to randomization
Inhaled anticholinergics	R03BB, R03AL01-07	≥1 claimed prescription	≤180 days prior to randomization
Inhaled glucocorticoids	R03BA, R03AK, R03AL08-09, R03AL11-12	≥1 claimed prescription	≤180 days prior to randomization
Insulin	A10A	≥1 claimed prescription	≤180 days prior to randomization
Non-insulin antidiabetic medication	A10B	≥1 claimed prescription	≤180 days prior to randomization
Systemic glucocorticoids	H02AB	≥1 claimed prescription	≤180 days prior to randomization
Immunosuppres-sants	L04	≥1 claimed prescription	≤180 days prior to randomization

Medication use at baseline will be assessed using ATC codes. ATC, Anatomic Therapeutical Chemical.

Prespecified Definitions for Prior Vaccinations at Baseline

Medication	ATC codes	Assessed as
Influenza vaccination in previous season	J07BB	Vaccinated in previous season (October 1 through May 31)
No. of influenza vaccinations in past 5 seasons	J07BB	No. of vaccinations in the past 5 seasons (assessed between October 1 through May 31 for each season)
Prior pneumococcal vaccination	J07AL	At least 1 vaccine after the age of 65
Prior COVID-19 vaccination	J07BX03	At least 1 vaccine received at any time prior to inclusion

Prior vaccination status will be assessed using ATC codes. ATC, Anatomic Therapeutical Chemical.

7.3. Endpoint assessment

All data used to assess endpoints during the study will be collected from regional administrative registries. Any hospitalization-based events with an associated COVID-19 ICD-10 discharge diagnosis code (B342, B972 – any position) will not be considered an eligible endpoint for assessment.

7.3.1. Primary endpoint

The primary endpoint of the study is the occurrence of a hospitalization due to influenza or pneumonia [composite endpoint]. The prespecified registry-based definition of the primary endpoint is as follows:

Endpoint	ICD-10 codes	Diagnosis type*	Inpatient/outpatient/minimum required length of stay/other criteria	Timeframe
Influenza or pneumonia hospitalization [composite endpoint]	J09-J18	A	Inpatient, at least 1 night	≥14 days after vaccination and up to May 31 the following year

* A = primary discharge diagnosis

7.3.2. Secondary endpoints

The secondary endpoints of the study are as follows:

1. Hospitalization for any cardio-respiratory disease [composite endpoint]
2. All-cause hospitalization
3. All-cause mortality
4. Hospitalization for influenza
5. Hospitalization for pneumonia

The prespecified registry-based definitions of the secondary endpoints are as follows:

Endpoint	**ICD-10 codes**	**Diagnosis type***	**Inpatient/outpatient/minimum required length of stay/other criteria**	**Timeframe**
Cardio-respiratory disease hospitalization** [composite endpoint]	I11, I13, I20-I25, I30-I31, I33, I38-I42, I46-I50, I60-I69, I74, J00-J06, J09-J18, J20-J22, J40-J47, J80-J81, J85-J86, J96	A	Inpatient, at least 1 night	≥14 days after vaccination and up to May 31 the following year
All-cause hospitalization	Any	Any	Inpatient, at least 1 night	≥14 days after vaccination and up to May 31 the following year

All-cause mortality	-	-	-	≥14 days after vaccination and up to May 31 the following year
Influenza hospitalization	J09-J11	A	Inpatient, at least 1 night	≥14 days after vaccination and up to May 31 the following year
Pneumonia hospitalization	J12-J18	A	Inpatient, at least 1 night	≥14 days after vaccination and up to May 31 the following year

* A = primary discharge diagnosis

** For cardio-respiratory hospitalizations, a broad list of ICD-10 codes is currently specified.

7.3.3. Exploratory endpoints

The exploratory endpoints of the study are as follows:

1. Hospitalization for influenza or pneumonia [composite endpoint] (alternate definition)
2. Hospitalization for pneumonia (alternate definition)
3. Hospitalization for influenza (alternate definition)
4. Hospitalization for any respiratory disease
5. Hospitalization for any cardiovascular disease
6. Hospitalization for myocardial infarction
7. Hospitalization for heart failure

8. Hospitalization for atrial fibrillation
9. Hospitalization for stroke
10. Major adverse cardiovascular events (MACE) defined as a composite of hospitalization for acute myocardial infarction, hospitalization for stroke, and cardiovascular death
11. MACE defined as a composite of hospitalization for acute myocardial infarction, hospitalization for stroke, hospitalization for heart failure, and cardiovascular death (alternate definition #1)
12. MACE defined as a composite of hospitalization for acute myocardial infarction, hospitalization for stroke, and all-cause death (alternate definition #2)
13. Hospitalization requiring mechanical ventilation
14. Laboratory-confirmed influenza
15. Laboratory-confirmed pneumococcal pneumonia
16. Laboratory-confirmed COVID-19
17. Cardio-respiratory mortality
18. Respiratory mortality
19. Cardiovascular mortality
20. In-hospital mortality

The prespecified registry-based definitions of the exploratory endpoints are as follows:

Endpoint	**ICD-10/ATC codes**	**Diagnosis type***	**Inpatient/outpatient/minimum required length of stay/other criteria**	**Timeframe**
Influenza or pneumonia hospitalization [composite endpoint] (alternate definition)	J09-J18	A or B	Inpatient, at least 1 night	≥14 days after vaccination and up to May 31 the following year
Influenza hospitalization	J09-J11	A or B	Inpatient, at least 1 night	≥14 days after

(alternate definition)				vaccination and up to May 31 the following year
Pneumonia hospitalization (alternate definition)	J12-J18	A or B	Inpatient, at least 1 night	≥14 days after vaccination and up to May 31 the following year
Respiratory disease hospitalization	J00-J06, J09-J18, J20-J22, J40-J47, J80-J81, J85-J86, J96	A	Inpatient, at least 1 night	≥14 days after vaccination and up to May 31 the following year
Cardiovascular disease hospitalization	I11, I13, I20-I25, I30-I31, I33, I38-I42, I46-I50, I60-I69, I74	A	Inpatient, at least 1 night	≥14 days after vaccination and up to May 31 the following year
Myocardial infarction hospitalization	I21	A	Inpatient, at least 1 night	≥14 days after vaccination and up to May 31 the following year
Heart failure hospitalization	I50	A	Inpatient, at least 1 night	≥14 days after vaccination and up to May 31 the following year

Atrial fibrillation hospitalization	I48	A	Inpatient, at least 1 night	≥14 days after vaccination and up to May 31 the following year
Stroke hospitalization	I63-I64	A	Inpatient, at least 1 night	≥14 days after vaccination and up to May 31 the following year
MACE	Hospitalizations: I21, I63-I64 Deaths: Any I-diagnosis as cause of death	For hospitalizations: A	For hospitalizations: Inpatient, at least 1 night	≥14 days after vaccination and up to May 31 the following year
MACE (alternate definition #1)	Hospitalizations: I21, I50, I63-I64 Deaths: Any I-diagnosis as cause of death	For hospitalizations: A	For hospitalizations: Inpatient, at least 1 night	≥14 days after vaccination and up to May 31 the following year
MACE (alternate definition #2)	Hospitalizations: I21, I63-I64 Deaths: All-cause	For hospitalizations: A	For hospitalizations: Inpatient, at least 1 night	≥14 days after vaccination and up to May 31 the following year
Hospitalization requiring mechanical ventilation	-	-	Any duration, procedural code "BGDA" registered at any point during hospitalization	≥14 days after vaccination and up to May 31 the

				following year
Laboratory-confirmed influenza	-	-	Positive influenza microbiology test	≥14 days after vaccination and up to May 31 the following year
Laboratory-confirmed pneumococcal pneumonia	-	-	Positive test for streptococcus pneumonia	≥14 days after vaccination and up to May 31 the following year
Laboratory-confirmed COVID-19	-	-	Positive COVID-19 test	≥14 days after vaccination and up to May 31 the following year
In-hospital mortality	-	-	Death (all-cause) while being hospitalized for ≥1 night	≥14 days after vaccination and up to May 31 the following year
Cardio-respiratory mortality	Any I- or J-diagnosis as cause of death	-	-	≥14 days after vaccination and up to May 31 the following year
Respiratory mortality	Any J-diagnosis as cause of death	-	-	≥14 days after vaccination and up to

				May 31 the following year
Cardiovascular mortality	Any I-diagnosis as cause of death	-	-	≥14 days after vaccination and up to May 31 the following year

* A = primary discharge diagnosis; B = secondary discharge diagnosis

7.3.4. Healthcare resource consumption endpoints

Healthcare resource consumption and associated costs will be evaluated according to the QIV-HD vs QIV-SD arms including, but not limited to:

1. Any hospital contacts
2. Hospitalizations requiring mechanical ventilation
3. Duration in days of hospitalization stays for:
    - Influenza or pneumonia
    - Any cardio-respiratory disease
    - Influenza
    - Pneumonia
4. Primary care visits
5. Anti-infective use

8. Safety monitoring

8.1. Risks and potential adverse reactions of the investigational treatment

The QIV-HD vaccine has received marketing approval for use in the trial study population and has a favorable safety profile. In general, the safety profile is similar to SD influenza vaccines[9,17]. Potential side effects are mainly limited to short-duration injection site pain, myalgia, headache and malaise, which is similar to SD influenza vaccines. HD influenza vaccines have already been used by the governmental vaccination program in persons aged 65 and above who were residents of nursing homes during the 2020/2021 influenza season, in persons aged 60 and above who were residents of nursing homes during 2021/2022 influenza season, and in the general population aged 85years or above in the 2022/2023 influenza season with no safety concerns. For further details regarding safety and potential risks, please refer to the enclosed QIV-HD product summary.

8.2. Risks and potential adverse reactions of the control treatment

The control treatment in this study will be the QIV-SD vaccine/vaccines procured by the General Public Health Directorate for use in the Influenza Regional Vaccination Program of Galicia. These vaccines will be administered to persons from the recruited age group seeking vaccination regardless of whether they choose to participate in the trial or not. Since we do not control which type or brand of vaccine participants who are randomized to the QIV-SD arm receive, safety considerations are not directly relevant.

8.3. Monitoring and reporting of adverse events and reactions

An adverse reaction (AR) is defined as any adverse and undesirable reaction that is causally related to the medicinal product regardless of dose. An adverse event (AE) is defined as any adverse event in a participant in a clinical trial following treatment with an investigational medicinal product. Since the treatments used in this trial are well-known and there has been sufficient data on non-serious adverse

events collected during clinical trials and post-marketing surveillance, we do not intend to collect data on non-serious AEs/ARs and only focus on monitoring and assessing serious adverse events (SAEs).

8.4. Monitoring and reporting of serious adverse events and reactions

An SAE is defined as an adverse event that results in death, is life-threatening, results in hospitalization or prolongs hospitalization, results in significant or persistent disability or incapacity, or leads to a congenital anomaly or malformation. A serious adverse reaction (SAR) is defined as an SAE which is assessed as related to an investigational product.

The occurrence of SAEs will be sought using a registry-based approach managed by the research team. Participants who are hospitalized for any cause or die during the study period will be identified from the regional administrative registries. For each participant randomized in a given season, one registry-based safety assessment will be performed 3 months (+/- 15 days) after vaccination.

At each safety assessment, all trial participants eligible for a safety assessment at that time according to their vaccination date will be assessed for SAEs (hospitalization for any cause or death) using a registry-based approach. Data from the Hospitalization registry in Galicia (SIHGA-sistema de información hospitalaria de Galicia) and the Galician Mortality Registry (Rexistro galego de mortalidade) will be obtained and crossed with the participants list to identify any hospitalization or death among the study participants. A list of study participants who have experienced an SAE will be produced from the registries using a pre-specified program designed for this purpose. The execution of the program, processing of the raw registry data and the production of this list for the safety assessment will be performed by the research team in a closed remote-access environment hosted on an encrypted Galician Health Data Authority server containing the raw registry data. Every SAE episode experienced by a trial participant identified through this method will be reviewed by a medical doctor included in the research

team using the electronic medical records of the participant. If a participant has been admitted to hospital but has not yet been discharged at the time of SAE assessment, or the SAE has not yet been resolved, and the SAE incident is deemed to be causally unrelated to study treatment by a medical doctor based on electronic medical record review, the event will be recorded as an SAE and no further follow-up of that particular incident will be made. Likewise, if a participant has been admitted to hospital, but has not yet been discharged at the time of SAE assessment, or the SAE has not yet been resolved, and the SAE incident is deemed to be causally related to study treatment by a medical doctor based on electronic medical record review, but the incident is a side effect mentioned in the product summary, the event will be recorded as an SAR and no further follow-up of that particular incident will be made. For all SAEs judged to be causally unrelated to study treatments, no other information than the personal identification number of the participant and the date of SAE occurrence will be recorded in the eCRF. For all SAEs judged to be causally related to study treatment, and thus considered SARs, which are side effects mentioned in the product summary, no other information than the personal identification number of the participant and the date of SAR occurrence will be recorded. The product summaries of the QIV-HD vaccine and the comparator QIV-SD vaccine(s) will be used to determine whether an SAR is unexpected and therefore possibly a suspected unexpected serious adverse reaction (SUSAR). Causality will be judged by a medical doctor included in the research team based on electronic medical record review. Life-threatening and fatal SUSARs must be registered and reported to the Spanish Agency for Drugs and Health as fast as possible and at the very latest within 7 days of the sponsor- principal investigator becoming aware of the incident. All other SUSARs are reported to and the EC within 15 days of the sponsor-principal investigator becoming aware of them. The number of SAEs, SARs and SUSARs recorded will be reported in both annual and final reports to the Spanish Agency for Drugs and Health and the Ethics Committee.

9. Statistical considerations

The statistical analyses will be performed by the trial sponsor. The final analyses to be performed will be described in the Statistical Analysis Plan (SAP), which will be finalized before registry data is first accessed.

9.1. Sample size calculation

The sample size needed for the assessment of the primary objective of the study is expected to be at least 114 011 participants and may be adjusted based on the interim analysis in order to maintain the likelihood of achieving approximately 830 cases of hospitalization for pneumonia and/or influenza for the primary endpoint. The population will be recruited during 2 influenza seasons, starting with at least 53,000 participants during the 2023/2024 season.

This required number of cases would provide at least 80% statistical power at final analysis to conclude on the primary objective under the following assumptions:

- The true rVE of QIV-HD to QIV-SD is 18% (assumption supported by prior findings[10,11]). The sample size was estimated assuming an 18% rVE which is included in the upper bound of the CI reported in prior findings[10,11] and is estimated to be the minimum rVE required to be cost-effective for the Galician public health authorities assuming the current price premium of the HD vaccine compared to the SD vaccine.
- An overall one-sided Type I error rate 0.025

By testing hypotheses at interim and final analysis, Type I error is increased and should be adjusted. One-sided alpha at first interim and final analysis will be computed using O'Brien-Fleming alpha spending function[18], and will depend on number of cases observed at first interim analysis (the exact alpha to be used at time of first interim and final analysis will be pre-specified in the SAP).

- QIV-HD will be considered superior to QIV-SD if the lower bound of the CI of rVE is > 0%
- An allocation ratio of QIV-HD to QIV-SD of 1:1
- An overall attack rate of 0,8% for the primary endpoint in the QIV-SD group
- Estimated attack rate based on 2022-2023 flu season Galician registry among vaccinated 65-79 years old[20,21]

9.2. Analysis sets

The primary analysis will be performed on the total of randomized participants included in the study (the intention-to-treat (ITT) set) using the ITT principle of analyzing participants according to their randomized group regardless of whether they received the intended treatment. For the primary and 1st secondary endpoints, a secondary analysis will be conducted using the as-treated set analyzing participants according to the vaccine administered. The as-treated set will also be used for analyzing safety events.

9.3. Influenza circulation threshold

In light of uncertain influenza epidemiology, an indicator of influenza viral activity will be used to assess whether influenza is circulating at sufficient levels to help inform the conduct of interim and/or final analyses. Based upon review of historical Galician surveillance data (sourced VIXIA) of laboratory testing for influenza, the specific threshold used for this study is defined as *at least four weeks (consecutive or non-consecutive) of ≥10% influenza test positivity during the observation period (October 1 to May 31 of each season). (*https://www.sergas.es/Saude-publica/vixilancia-epidemioloxica-da-gripe*)*. The threshold will be used as described in sections 9.4.1 and 9.5.

9.4. Interim analysis and sample size adjustment

Due to the unpredictable epidemiology of influenza, the sample size and/or the duration of the study may be adjusted in order to maintain the likelihood of achieving the expected number of cases for the primary endpoint (pneumonia and/or influenza hospitalizations).

A prespecified interim analysis will be performed immediately after completion of follow-up for clinical endpoints for the 2023-2024 season (follow-up completed on May 31, 2024) by the sponsor. The study may stop for superior efficacy if the primary objective is demonstrated (see section 9.7.1) using adjusted one-sided alpha calculated for first interim analysis; however, in that case, the sponsor may decide to continue the study through a second season to assess the reliability of findings.

Under the assumptions considered for sample size calculation and by using O'Brien Fleming alpha spending function, the probability of concluding at interim analysis is low ; therefore, the risk of discrepancy between interim and final analyses (i.e. conclusive at interim and inconclusive at final) is limited.

No stopping rule for futility is planned.

Apart from sample size adjustment, no further modifications to study conduct or analysis will be implemented based on interim analysis results.

9.4.1. Dependency on influenza circulation threshold

The full interim analysis, including testing for superiority, will **only** be performed if the influenza circulation threshold is met during the first season (2023/2024). If the threshold is not met, then only the total number of primary endpoint cases will be assessed, as to be able to adjust the sample size for the second season.

9.5. Testing procedure for the final analyses

The population analyzed and the testing procedures will depend on whether influenza circulation reaches the threshold specified in section 9.2 during the first and/or second season. Possible scenarios and corresponding analysis approaches are detailed below.

9.5.1. Hierarchical testing sequence

The final analyses will be performed according to the following hierarchical order:

Endpoint	**Rank in hierarchical testing sequence**
Primary endpoint: Hospitalization for influenza or pneumonia [composite endpoint]	1
Secondary endpoint #1: Hospitalization for any cardio-respiratory disease [composite endpoint]	2
Secondary endpoint #2: All-cause hospitalization	3
Secondary endpoint #3: All-cause mortality	4

9.5.2. Procedure if threshold is reached during BOTH seasons:

If the influenza circulation threshold is reached during BOTH seasons, the full study population will be used for the final analysis. The primary and secondary endpoints (#1-3) will be evaluated using the hierarchical testing sequence specified in section 9.5.1. First, the primary endpoint will be tested by using the adjusted alpha for final analysis, defined at time of first interim analysis; if the null hypothesis is rejected, then testing of the subsequent secondary endpoints will continue down the hierarchy with the adjusted alpha. Testing of the secondary endpoints will continue sequentially until a null hypothesis is not rejected in which case the remaining endpoints in the testing sequence will be assessed descriptively only. If the null hypothesis for the primary endpoint is not rejected, no formal hypothesis testing will be

conducted for the secondary endpoints, and these endpoints will be assessed descriptively only. All other endpoints will be assessed descriptively only.

9.5.3. Procedure if threshold is reached during the FIRST season ONLY:

If the influenza circulation threshold is reached during the FIRST season ONLY (2023/2024), only the data collected during the first season will be used for the final analysis. The primary and secondary endpoints (#1-3) will be evaluated using the hierarchical testing sequence specified in section 9.5.1. First, the primary endpoint will be tested at a one-sided alpha level of 0.025 (as no additional alpha would have been spent on new analysis beyond the first season in this scenario); if the null hypothesis is rejected, then testing of the subsequent secondary endpoints will continue down the hierarchy at a one-sided alpha level of 0.025. Testing of the secondary endpoints will continue sequentially until a null hypothesis is not rejected in which case the remaining endpoints in the testing sequence will be assessed descriptively only. If the null hypothesis for the primary endpoint is not rejected, no formal hypothesis testing will be conducted for the secondary endpoints, and these endpoints will be assessed descriptively only. All other endpoints will be assessed descriptively only. Descriptive analyses with regards to data collected during the 2nd season (independently and/or pooled with 1st season data) may also be conducted.

9.5.4. Procedure if threshold is reached during the SECOND season ONLY:

If the influenza circulation threshold is reached during the SECOND season ONLY (2024/2025), only the data collected during the second season will be used for the final analysis. Assuming sample size adjustment following the 1st season and sufficient participant recruitment during the second season, the primary and secondary endpoints (#1-3) will be evaluated using the hierarchical testing sequence specified in section 9.5.1. First, the primary endpoint will be tested at a one-sided alpha level of 0.025 (as no alpha would have been spent on an interim analysis in this scenario); if the null hypothesis is

rejected, then testing of the subsequent secondary endpoints will continue down the hierarchy at a one-sided alpha level of 0.025. Testing of the secondary endpoints will continue sequentially until a null hypothesis is not rejected in which case the remaining endpoints in the testing sequence will be assessed descriptively only. If the null hypothesis for the primary endpoint is not rejected, no formal hypothesis testing will be conducted for the secondary endpoints, and these endpoints will be assessed descriptively only. All other endpoints will be assessed descriptively only. Descriptive analyses with regards to data collected during the 1st season (independently and/or pooled with 2nd season data) may also be conducted.

9.5.5. Procedure if threshold is NOT reached during EITHER of the 2 seasons:

If the influenza circulation threshold is NOT reached during EITHER of the 2 seasons (2023/2024 and (2024/202), a descriptive final analysis will be conducted across the full study population, where all endpoints will be analyzed descriptively only.

Note: pending on whether the influenza circulation threshold is met in any of the seasons, the sponsor may also choose to extend the study period by an additional season and increase the sample size accordingly.

9.6. Subgroup analyses

The consistency of the rVE estimates will be tested across the following prespecified subgroups:

1. Age: ≥median vs. <median
2. Age: 65-69 years vs. 70-74 years vs. 75-79 years
3. Presence of at least one chronic disease: Yes vs no
4. Chronic lung disease: Yes vs. no
    - Chronic obstructive pulmonary disease: Yes vs. no
    - Asthma: Yes vs. no

5. Chronic cardiovascular disease: Yes vs. no
    - Ischemic heart disease: Yes vs. no
    - Heart failure: Yes vs. no
    - Atrial fibrillation: Yes vs. no
6. Diabetes: Yes vs. no
7. Cancer: Yes vs. no
8. Immunodeficiency: Yes vs. no
9. Vaccination scheme: Vaccinated with QIV-HD in both seasons vs. vaccinated with QIV-SD in both seasons vs. vaccinated with QIV-HD in season 1 and QIV-SD in season 2 vs. vaccinated with QIV-SD in season 1 and QIV-HD in season 2 (only events accrued during the second season will be considered for this analysis)

The division of the population into subgroups will be made according to the definitions specified in section 7.2.

9.7. Statistical analysis

Continuous baseline variables will be summarized using means and standard deviations or medians and interquartile ranges. Binary or categorical variables will be compared using frequencies and proportions. Unless otherwise specified, p-values <0.05 (including alpha-adjustment if required) will be considered statistically significant. Full details of the statistical analysis will be described in the SAP.

9.7.1. Relative vaccine effectiveness (rVE)

For rVE calculations, only the participants' first events in each endpoint category will be considered.

rVE will be calculated as:

$$rVE = (1-(C_{HD} /N_{HD})/(C_{SD}/N_{SD})) \times 100\%$$

Where:

C_{HD}: describes the number of cases in the QIV-HD arm

N_{HD}: describes the number of participants in the QIV-HD arm

C_{SD}: describes the number of cases in the QIV-SD arm

N_{SD}: describes the number of participants in the QIV-SD arm

For all endpoints, an rVE point estimate and a 95%/alpha-adjusted confidence interval (CI) will be reported. p-values will only be reported for endpoints tested in the hierarchical testing procedure. The confidence interval (CI) will be calculated using the Clopper-Pearson method[22]. Inference will be based on the lower limit of the alpha-adjusted CIs. QIV-HD will be considered superior to QIV-SD if the lower bound of the estimated rVE alpha-adjusted CI is >0.

9.7.2. Sensitivity analyses

The following sensitivity analyses will be performed:

1. Calculating rVE using an extended follow-up period until August 31 the following year
2. Calculating rVE using a follow-up period restricted to the peak of the influenza season (according to a prespecified definition – to be defined in the SAP)
3. Analyzing the endpoints using survival analysis instead of the rVE approach, i.e. time-to-first-event and Cox proportional hazards regression
4. Analyzing the primary and secondary endpoints without excluding endpoints that have an associated COVID-19 discharge diagnosis code
5. An analysis of the primary and secondary endpoints based on a model accounting for potential within-participant correlation in participants enrolled in >1 season

6. Calculating rVE using a follow-up period defined as from the time of randomization until May 31 the following year

9.7.3. Additional prespecified analyses

Details of all prespecified analyses will be described in the SAP.

1. Analyzing the total number of endpoint events (first and recurrent) instead of first event only.
2. Temporal rVE analysis: The cumulative number of events will be assessed on a weekly basis enabling calculation of weekly cumulative rVE estimates. The estimates will be descriptively compared to influenza circulation levels.

9.8. Pooled/federated analysis

Deidentified data from this study may be combined with data from other, similar studies in pooled and/or federated analyses. These analyses, including data governance, will be described in a separate study protocol, and only carried out after having received ethics committee approval.

10. Administrative and legal obligations

10.1. Ethical considerations

The study will be subject to approval by Ethics Committee of reference and the competent authority before its implementation. The study will adhere to the principles of the Declaration of Helsinki and undergo monitoring according to the International Conference on Harmonization guidelines for Good Clinical Practice. The study will be registered in the European Union Clinical Trials Register and on Clinicaltrials.gov.

The safety profile of the QIV-HD vaccine is similar to the SD vaccines currently used, with the exception of increased mild to moderate local reactions in some HD recipients[8]. Furthermore, the QIV-HD vaccine

has already been approved for clinical use in persons aged 60+ years, has previously been used (funded through Influenza Regional Vaccination Program of Galicia) among community-dwelling adults aged 85+ as well as those aged 60+ living in nursing homes in the 2022/2023 influenza season. Given that evidence indicates that the HD vaccine is superior to the SD vaccine for preventing influenza infection and hospitalizations in the 65+ age group, it is likely that the decision to only offer the vaccine to citizens aged 80+ (an age group which is arguably more frail than the 65-79 years age group) and not all citizens aged 65+ is based on costs, since the HD vaccine is approx. twice as expensive as the SD vaccine. Furthermore, approximately 65% of US citizens aged 65+ receive this vaccine annually. This study offers the benefit of providing the QIV-HD vaccine to Galician citizens who would not be offered this opportunity under the standard governmental vaccination program. Given these considerations, we believe this trial involves minimal risk to the individual patient and that participation in the trial is not associated with an increased risk of adverse outcomes as compared to simply undergoing vaccination as part of the Influenza Regional Vaccination Program of Galicia.

10.2. Trial monitoring

This trial will be monitored by the Clinical Trials Unit of the sponsor sited in the Hospital Clínico Universitario de Santiago de Compostela.

10.3. Funding

This protocol has been co-developed with Sanofi. Sanofi will provide the QIV-HD doses required for this trial free of charge (approximately 27.000 doses/season). In addition, Sanofi will be funding the trial to cover for all expenses associated with the trial.

10.4. Publication of results

Both negative, positive, and inconclusive results will be submitted for publication in peer-reviewed journals. Authorship criteria will be based on Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals by The International Committee of Medical Journal Editors. The results of the study will be published on Clinicaltrials.gov and in the CTIS database.

10.5. Insurance

The study is considered a low-intervention clinical trial so patients will be covered by normal patient insurance. No additional insurance policy is required.

11. References

1. Influenza (seasonal)https://www.who.int/westernpacific/health-topics/influenza-seasonal (28 June 2023)

2. Iuliano AD, Roguski KM, Chang HH, Muscatello DJ, Palekar R, Tempia S, Cohen C, Gran JM, Schanzer D, Cowling BJ, Wu P, Kyncl J, Ang LW, Park M, Redlberger-Fritz M, Yu H, Espenhain L, Krishnan A, Emukule G, Asten L van, Silva SP da, Aungkulanon S, Buchholz U, Widdowson M-A, Bresee JS. Estimates of global seasonal influenza-associated respiratory mortality: a modelling study. *Lancet Lond Engl* 2018;**391**:1285–1300.

3. Lafond KE, Porter RM, Whaley MJ, Suizan Z, Ran Z, Aleem MA, Thapa B, Sar B, Proschle VS, Peng Z, Feng L, Coulibaly D, Nkwembe E, Olmedo A, Ampofo W, Saha S, Chadha M, Mangiri A, Setiawaty V, Ali SS, Chaves SS, Otorbaeva D, Keosavanh O, Saleh M, Ho A, Alexander B, Oumzil H, Baral KP, Huang QS, Adebayo AA, Al-Abaidani I, Horoch M von, Cohen C, Tempia S, Mmbaga V, Chittaganpitch M, Casal M, Dang DA, Couto P, Nair H, Bresee JS, Olsen SJ, Azziz-Baumgartner E, Nuorti JP, Widdowson M-A. Global burden of influenza-associated lower respiratory tract infections and hospitalizations among adults: A systematic review and meta-analysis. *PLoS Med* 2021;**18**:e1003550.

4. https://www.cdc.gov/flu/highrisk/index.htm (29 June 2023)

5. https://www.ecdc.europa.eu/en/seasonal-influenza/prevention-and-control/vaccines/risk-groups (29 June 2023)

6. Gross PA, Hermogenes AW, Sacks HS, Lau J, Levandowski RA. The Efficacy of Influenza Vaccine in Elderly Persons. *Ann Intern Med* 1995;**123**:518–527.

7. Govaert ThME, Thijs CTMCN, Masurel N, Sprenger MJW, Dinant GJ, Knottnerus JA. The Efficacy of Influenza Vaccination in Elderly Individuals: A Randomized Double-blind Placebo-Controlled Trial. *JAMA* 1994;**272**:1661–1665.

8. Falsey AR, Treanor JJ, Tornieporth N, Capellan J, Gorse GJ. Randomized, Double-Blind Controlled Phase 3 Trial Comparing the Immunogenicity of High-Dose and Standard-Dose Influenza Vaccine in Adults 65 Years of Age and Older. *J Infect Dis* 2009;**200**:172–180.

9. DiazGranados CA, Dunning AJ, Kimmel M, Kirby D, Treanor J, Collins A, Pollak R, Christoff J, Earl J, Landolfi V, Martin E, Gurunathan S, Nathan R, Greenberg DP, Tornieporth NG, Decker MD, Talbot HK. Efficacy of High-Dose versus Standard-Dose Influenza Vaccine in Older Adults. *N Engl J Med* 2014;**371**:635–645.

10. DiazGranados CA, Robertson CA, Talbot HK, Landolfi V, Dunning AJ, Greenberg DP. Prevention of serious events in adults 65 years of age or older: A comparison between high-dose and standard-dose inactivated influenza vaccines. *Vaccine* 2015;**33**:4988–4993.

11. Lee JKH, Lam GKL, Yin JK, Loiacono MM, Samson SI. High-dose influenza vaccine in older adults by age and seasonal characteristics: Systematic review and meta-analysis update. Vaccine X. 2023 Jun 5;14:100327.

12. Gravenstein S, Davidson HE, Taljaard M, Ogarek J, Gozalo P, Han L, Mor V. Comparative effectiveness of high-dose versus standard-dose influenza vaccination on numbers of US nursing home residents admitted to hospital: a cluster-randomised trial. *Lancet Respir Med* 2017;**5**:738–746.

13. Johansen ND, Modin D, Nealon J, Samson S, Salamand C, Loiacono MM, Larsen CS, Jensen AM, Landler NE, Claggett BL, Solomon SD. A Pragmatic Randomized Feasibility Trial of Influenza Vaccines. NEJM Evidence. 2023 Jan 24;2(2).

14. https://www.sergas.es/Saude-publica/vixilancia-epidemioloxica-da-gripe

15. FDA. Guidance for Industry: Clinical Data Needed to Support the Licensure of Seasonal Inactivated Influenza Vaccines. **2007**.

16. James S, Rao SV, Granger CB. Registry-based randomized clinical trials—a new clinical trial paradigm. *Nat Rev Cardiol* 2015;**12**:312–316.

17. Chang L-J, Meng Y, Janosczyk H, Landolfi V, Talbot HK. Safety and immunogenicity of high-dose quadrivalent influenza vaccine in adults ≥65 years of age: A phase 3 randomized clinical trial. *Vaccine* 2019;**37**:5825–5834.

18. O'Brien PC, Fleming TR. A Multiple Testing Procedure for Clinical Trials. *Biometrics* 1979;**35**:549–556.

19. Lewis NM, Chung JR, Uyeki TM, Grohskopf L, Ferdinands JM, Patel MM. Interpretation of Relative Efficacy and Effectiveness for Influenza Vaccines. *Clin Infect Dis* 2021:ciab1016.

20. https://www.cdc.gov/flu/weekly/overview.htm

21. https://www.isciii.es/QueHacemos/Servicios/VigilanciaSaludPublicaRENAVE/EnfermedadesTransmisibles/Documents/GRIPE/Informes%20semanales/Temporada_2022-23/Informe%20semanal_SiVIRA_032023.pdf

22. Newcombe RG. Two-sided confidence intervals for the single proportion: comparison of seven methods. *Stat Med* 1998;**17**:857–872.