PASS INFORMATION

Title	**Prospective non-interventional cohort study to assess safety and tolerability of 3Fluart 2015/2016 trivalent seasonal influenza vaccine in children, adolescents, adults and elderly subjects**
Protocol version identifier	v03
Date of last version of protocol	07 October 2015

EU PAS register number	ENCEPP/SDPP/10350
Active substance	6µg HA per 0.5 ml vaccine per the following influenza virus strains: - Influenza virus Type A H1N1, whole virion, inactivated [A/California/7/2009 (H1N1)pdm09-like strain (A/California/7/2009, NYMC X-181)] [1] - Influenza virus Type A H3N2, whole virion, inactivated [A/Switzerland/9715293/2013 (H3N2)-like strain (A/Switzerland/9715293/2013, NIB-88)][1] - Influenza virus Type B, whole virion, inactivated [B/Phuket/3073/2013-like strain (B/Phuket/3073/2013 (wild type))][1] [1]Strains recommended by the BWP ad-hoc influenza Working Party of the CHMP to be incorporated in trivalent vaccines used in the upcoming seasonal epidemics on the Northern Hemisphere ATC code: J07BB01
Medicinal product	3Fluart suspension for injection (influenza vaccine, whole virion, inactivated) for season 2015/2016 (i.e. 3Fluart 2015/2016 vaccine in the followings)
Product reference	-
Procedure number	3Fluart-H-18
Marketing authorisation holder(s)	Fluart Innovative Vaccines Ltd.
Joint PASS	No

Title	**Prospective non-interventional cohort study to assess safety and tolerability of 3Fluart 2015/2016 trivalent seasonal influenza vaccine in children, adolescents, adults and elderly subjects**
Protocol version identifier	v03
Date of last version of protocol	07 October 2015

Research question and objectives	The aim of this observational study, is to detect a potential increase in reactogenicity and allergic events that is intrinsic to the product in near real-time as part of the active surveillance of subjects vaccinated with 3Fluart vaccine containing influenza virus strains recommended for the 2015/2016 seasonal epidemics in accordance with the Summary of Product Characteristics. **Objectives**: - To evaluate the occurrence of defined Adverse Events of Interests (AEIs) and other Adverse Events (AEs) in vaccinated subjects participating in the study. - To rapidly detect any clinically significant change compared to what was known or expected with the previous vaccine compositions in the frequency and severity of Adverse Reactions (ARs) in vaccinated subjects participating in the study.
Country(-ies) of study	Hungary
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MARKETING AUTHORIZATION HOLDER(S)

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2. LIST OF ABBREVIATIONS

AE	Adverse Event
AR	Adverse Reaction
AEI	Adverse Event of Interest
GCP	Good Clinical Practice
HA	Hemagglutinin
OGYÉI	Országos Gyógyszerészeti és Élelmezés-egészségügyi Intézet (National Institute of Pharmacy and Nutrition, Hungary)
MedDRA	Medical Dictionary for Regulatory Affairs
PRAC	Pharmacovigilance Risk Assessment Committee
PT	Preferred Term
SmPC	Summary of Product Characteristics
SOC	System Organ Class
ETT-TUKEB	Egészségügyi Tudományos Tanács - Tudományos és Kutatásetikai Bizottság (Ethics Committee)
WHO	World Health Organisation

3. RESPONSIBLE PARTIES

TITLE: Prospective non-interventional cohort study to assess safety and tolerability of 3Fluart 2015/2016 trivalent seasonal influenza vaccine in children, adolescents, adults and elderly subjects.

Undersigned below agree to adhere to the Study Protocol as approved by the National Institute of Pharmacy and Nutrition (OGYÉI) and Ethics Committee (ETT-TUKEB). This study will be conducted in accordance with principles laid down in Declaration of Helsinki, local ethical and legal requirements.

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Date: 09/10/2015 Signature:

TITLE: Prospective non-interventional cohort study to assess safety and tolerability of 3Fluart 2015/2016 trivalent seasonal influenza vaccine in children, adolescents, adults and elderly subjects.

Undersigned below agree to adhere to the Study Protocol as approved by the National Institute of Pharmacy and Nutrition (OGYÉI) and Ethics Committee (ETT-TUKEB). This study will be conducted in accordance with principles laid down in Declaration of Helsinki, local ethical and legal requirements.

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4. ABSTRACT

Title	**Prospective non-interventional cohort study to assess safety and tolerability of a 3Fluart 2015/2016 trivalent seasonal influenza vaccine in children, adolescents, adults and elderly subjects**
Version	v03
Date	07 October 2015

Name and affiliation of main author	Orsolya Gyurján PharmD Study director, Clinical Safety Officer, Deputy QPPV Fluart Innovative Vaccines Ltd.
Rationale and background	Seasonal influenza vaccines present several specific challenges for pharmacovigilance. These include mass immunisation in large population cohorts in a relatively short and fixed time period each year, seasonal factors (e.g. differentiating seasonal peaks in background illness from vaccine-induced effects) and multiplicity of seasonal vaccine products on the market with need for product-specific surveillance. With regard to the provisions of *Interim guidance on enhanced safety surveillance for seasonal influenza vaccines in the EU*, active surveillance of 3Fluart vaccine is to be performed right after the product is placed on the market in frames of the present non-interventional cohort study. The seasonal trivalent influenza vaccine with reduced active substance content, grown in embryonated hen's egg, inactivated and adjuvanted has the first season on the market, though, according to the clinical trials performed, vaccine efficacy and safety has been widely confirmed. Further, the vaccine contains 6µg HA per Type A/H1N1, Type A/H3N2 and Type B influenza virus strains and is manufactured with a well-established technology used for years with regard to Fluval AB suspension for injection containing 15µg HA per strain.

Title	**Prospective non-interventional cohort study to assess safety and tolerability of a 3Fluart 2015/2016 trivalent seasonal influenza vaccine in children, adolescents, adults and elderly subjects**
Version	v03
Date	07 October 2015

Research question and objectives	The aim of this observational study, which will be initiated right after 3Fluart 2015/2016 seasonal influenza vaccine is licensed and used in a mass vaccination campaign, is to detect a potential increase in reactogenicity and allergic events that is intrinsic to the product in near real-time aiming to mitigate risks before the peak period of seasonal immunisation. The objectives are to evaluate the occurrence of defined Adverse Events of Interests (AEIs) and other Adverse Events (AEs) in vaccinated subjects participating in the study and to rapidly detect any clinically significant change compared to what was known or expected with the previous vaccine compositions in the frequency and severity of Adverse Reactions (ARs) in vaccinated subjects participating in the study.
Study design	Defined cohorts of children and adults will be actively followed-up seven (7) days after immunisation for AEIs and other AEs following vaccination, with the aim to detect eventual changes in the frequency and severity of related events. Patients will be vaccinated according to the Summary of Product Characteristics (SmPC), in compliance with national vaccination policy decisions in Hungary and standard practice, then, will be involved into the study by signing the patient information and informed consent and forms. Relevant information on AEs will be collected during a follow-up phone contact seven (7) days after vaccination. The duration of the study on a patient basis will be seven (7) days. The study will be conducted in multiple study centres in Hungary.

Title	**Prospective non-interventional cohort study to assess safety and tolerability of a 3Fluart 2015/2016 trivalent seasonal influenza vaccine in children, adolescents, adults and elderly subjects**
Version	v03
Date	07 October 2015

Population	Patients will be vaccinated according to the SmPC, in compliance with national vaccination policy decisions in Hungary and standard practice, then, will be involved into the study. Planned minimum and maximum numbers of the study are defined as follows: hundred (100) – hundred and twenty (120) per children aged 3-12 years, hundred (100) – hundred and twenty (120) per age group of adolescents aged 13-17 years, hundred and fifty (150) –hundred and eighty (180) per adults aged 18-65 years and hundred and fifty (150) –hundred and eighty (180) per elders aged over 65 years.
Variables	The occurrence rates of AEIs as well as other reported AEs will be evaluated. The following AEIs (i.e. reactogenicity endpoints) are defined: - Vaccinaton site pain - Vaccination site erythema - Vaccination site swelling - Vaccination site induration - Vaccination site haematoma - Urticaria - Erythema - Headache - Fever - Malaise - Chills - Fatigue - Hyperhidrosis - Pallor - Dizziness - Numbness - Dysphonia - Nausea - Myalgia - Arthralgia - Pain in extremity - Hypersensitivity reactions, including ocular symptoms - Use of medicines available without prescription to treat pain and fever

Title	**Prospective non-interventional cohort study to assess safety and tolerability of a 3Fluart 2015/2016 trivalent seasonal influenza vaccine in children, adolescents, adults and elderly subjects**
Version	v03
Date	07 October 2015

Data sources	Data Report Forms will be available for data recording. However, source data will be available to document the existence of the subject and substantiate integrity of study data collected.
Study size	A maximum of six hundred (600) and a minimum of five hundred (500) male and female subjects will be vaccinated with 3Fluart vaccine containing influenza virus strains recommended for the 2015/2016 seasonal epidemics in accordance with the SmPC and involved into the study as between the following planned numbers by age groups: - Children aged 3-12 years: hundred (100) – hundred and twenty (120); - Adolescents aged 13-17 years: hundred (100) – hundred and twenty (120); - Adults aged 18-65 years: hundred and fifty (150) – hundred and eighty (180) subjects; - Elders aged over 65 years: hundred and fifty (150) – hundred and eighty (180) subjects.

Title	**Prospective non-interventional cohort study to assess safety and tolerability of a 3Fluart 2015/2016 trivalent seasonal influenza vaccine in children, adolescents, adults and elderly subjects**
Version	v03
Date	07 October 2015

Data analysis	All individual data will be listed. Every subject who has already been vaccinated and involved in the study will be included in the statistical analysis. AEs will be coded using MedDRA dictionary. The assessment of safety and tolerability will be primarily based on the occurrence rates of adverse reactions. The occurrence rates of adverse reactions will be summarized by SOC (System Organ Class) and PT (Preferred Term) and compared to what was already known or expected with 3Fluart vaccine as follows: - Evaluation of the occurrence of AEIs and other AEs in vaccinated subjects participating in the study. Occurrence rate of each AE will be presented by age group and severity. - Rapid detection of any clinically significant change compared to what was known or expected with the previous vaccine compositions in the frequency and severity of ARs in vaccinated subjects participating in the study. Comparison will be performed between ARs of the study and ARs observed in the last clinical trial performed with 3Fluart influenza vaccine; further, between ARs of the study and with those defined in the SmPC of 3Fluart influenza vaccine.

Title	**Prospective non-interventional cohort study to assess safety and tolerability of a 3Fluart 2015/2016 trivalent seasonal influenza vaccine in children, adolescents, adults and elderly subjects**
Version	v03
Date	07 October 2015

Milestones	Planned milestones of the study: **Start of data collection:** The date from which information on the first study subject vaccinated with 3Fluart influenza vaccine is first recorded in the study dataset at the beginning of the vaccination campaign. **End of data collection:** The date of fulfilment of the planned study size, in approximately one (1) month after the start of data collection. **Weekly Summary Safety Reports:** Weekly during the follow up period of subjects. **Expedited Summary Safety Report:** In one (1) month after the start of data collection. **Final Study Report:** In six (6) months after the end of data collection.

5. AMENDMENTS AND UPDATES

Number	Date	Section of the study protocol	Amendment or update	Reason
1.	17 August 2015	PASS Information	Incorporation of EU PAS Register Number.	N/A
2.	17 August 2015	6. Milestones	Correction of end of data collection: "the date of fulfilment of the planned study size in approximately one (1) month after the start of data collection" instead of "in approximately one (1) month after the start of data collection".	Request of OGYÉI (*OGYI/28748-2/2015, 13 August 2015*)
3.	17 August 2015	9. Research methods: 9.3. Variables	Incorporation of the following AEIs as variables: "hypersensitivity reactions, including ocular symptoms" and "use of medicines available without prescription to treat pain and fever".	Request of OGYÉI (*OGYI/28748-2/2015, 13 August 2015*)
4.	17 August 2015	11. Management and reporting of adverse events / adverse reactions	Incorporation of defined AEIs ("hypersensitivity reactions, including ocular symptoms" and "use of medicines available without prescription to treat pain and fever") to parts "Definition of AEIs" and "Definition for the assessment of severity".	Due to the request of OGYÉI (*OGYI/28748-2/2015, 13 August 2015*)
5.	17 August 2015	Annex 1. List of stand-alone documents: Data Report Forms	Incorporation of defined AEIs ("hypersensitivity reactions, including ocular symptoms" and "use of medicines available without prescription to treat pain and fever") to Data Report Forms.	Due to the request of OGYÉI (*OGYI/28748-2/2015, 13 August 2015*)
6.	07 October 2015	Annex 1. List of stand-alone documents: Data Report Forms, Patient Informations, Informed Consents	Harmonisation forms with legislation laid down in *23/2002. (V.9.) EüM rendelet*. New Patient Information and Informed Consent for patients aged 3-6 years.	Due to the request of ETT TUKEB (*46260-1/2015/EKU, 02 October 2015)*

6. MILESTONES

Milestone	Planned date
Start of data collection	The date from which information on the first study subject vaccinated with 3Fluart influenza vaccine is first recorded in the study dataset at the beginning of the vaccination campaign.
End of data collection	The date of fulfilment of the planned study size, in approximately one (1) month after the start of data collection.
Weekly Summary Safety Reports	Weekly during the follow up period of subjects.
Expedited Summary Safety Report	In one (1) month after the start of data collection.
Final Study Report	In six (6) months after the end of data collection.

7. RATIONALE AND BACKGROUND

Influenza is a viral infection that affects mainly the nose, throat, bronchi and, occasionally, lungs. Infection usually lasts for about a week, and is characterized by sudden onset of high fever, aching muscles, headache and severe malaise, non-productive cough, sore throat and rhinitis. Most infected people recover within one to two weeks without requiring medical treatment. Prophylaxis of influenza by vaccination is considered the first and best way of protection. The National Centre for Epidemiology recommends that sub-populations at risk of severe complications on influenza are vaccinated yearly.

Seasonal influenza vaccines present several specific challenges for pharmacovigilance. These include mass immunisation in large population cohorts in a relatively short and fixed time period each year, seasonal factors (e.g. differentiating seasonal peaks in background illness from vaccine-induced effects) and multiplicity of seasonal vaccine products on the market with need for product-specific surveillance. There have also been examples when product-specific (or batch-specific) changes in quality specifications, arising from changes to a manufacturing process during the product life-cycle, have led to an unexpected change in reactogenicity or other adverse immune response. Due to these challenges, pharmacovigilance systems for influenza vaccines need capability to rapidly detect and evaluate potential new safety concerns each influenza season. The aim is to mitigate risks before the peak period of seasonal immunisation (i.e. at least within the first month after the start of immunisation).

With regard to the provisions of *Interim guidance on enhanced safety surveillance for seasonal influenza vaccines in the EU*, active surveillance is to be performed right after the product is placed on the market in frames of the present non-interventional cohort study.

The seasonal trivalent influenza vaccine with reduced active substance content, grown in embryonated hen's egg, inactivated and adjuvanted has the first season on the market, though, according to the clinical trials performed, vaccine efficacy and safety has been widely confirmed. Further, the vaccine contains 6µg HA per Type A/H1N1, Type A/H3N2 and Type B influenza virus strains and is manufactured with a well-established technology used for years with regard to Fluval AB suspension for injection containing 15µg HA per strain.

8. RESEARCH QUESTION AND OBJECTIVES

The aim of this observational study, which will be initiated right after 3Fluart 2015/2016 seasonal influenza vaccine is licensed and used in a mass vaccination campaign, is to detect a potential increase in reactogenicity and allergic events that is intrinsic to the product in near real-time aiming to mitigate risks before the peak period of seasonal immunisation.

Objectives:

- To evaluate the occurrence of defined AEIs and other AEs in vaccinated subjects participating in the study;
- To rapidly detect any clinically significant change compared to what was known or expected with the previous vaccine compositions in the frequency and severity of ARs in vaccinated subjects participating in the study.

9. RESEARCH METHODS

9.1. Study design

This is a prospective, non-interventional, cohort, non-randomized, open-label study.

The aim of the vaccination is to reduce the morbidity associated with seasonal influenza infection. Defined cohorts of children and adults previously vaccinated with a single dose of 3Fluart suspension for injection (influenza vaccine, whole virion, inactivated, adjuvanted) will be actively followed-up seven (7) days after immunisation for defined AEIs and other AEs following vaccination, with the aim to detect eventual changes in the frequency and severity of related events.

9.2. Setting

In accordance with the provisions of guide *Interim guidance on enhanced safety surveillance for seasonal influenza vaccines in the EU*, further, based on the planed size of the study conducted in the previous year (i.e. Study FluvalAB-H-17), a maximum of six hundred (600) and a minimum of five hundred (500) subjects vaccinated with a single dose of 3Fluart vaccine containing influenza virus strains recommended for the 2015/2016 seasonal epidemics in accordance with the SmPC will be involved into the study as between the following planned numbers by age groups:

- Children aged 3-12 years: hundred (100) – hundred and twenty (120) subjects;
- Adolescents aged 13-17 years: hundred (100) – hundred and twenty (120) subjects;
- Adults aged 18-65 years: hundred and fifty (150) – hundred and eighty (180) subjects;
- Elders aged over 65 years: hundred and fifty (150) – hundred and eighty (180) subjects.

The study is planned to be initiated right after 3Fluart suspension for injection is placed on the market.

Patients will be vaccinated according to the SmPC, in compliance with national vaccination policy decisions in Hungary and standard practice, then, will be involved into the study by signing the patient information and informed consent and forms.

Relevant information on AEs will be collected during a follow-up phone contact seven (7) days after vaccination and documented on Data Report Forms.

The duration of the study on a patient basis will be seven (7) days. Weekly reports (i.e. Weekly Summary Safety Reports) are planned to be submitted on data of every week's follow up. Further, summary reports (i.e. Expedited Summary Safety Report and Final Study Report) are planned to submitted, including cumulative safety data of the study analysed with descriptive and comparative statistics.

The study will be conducted in multiple study centres in Hungary listed in a stand-alone document (i.e. List of investigators).

9.2.1. Vaccination

The inclusion of subjects in this study will follow national vaccination policy decisions in Hungary and standard practise. Inclusion criteria will consist of the followings:

- subjects who have already received a dosage of 3Fluart 2015/2016 vaccine according to the SmPC;
- subjects willing to participate in the study expressed by signing the patient information and informed consent and forms right after vaccination with 3Fluart 2015/2016 vaccine is performed.

9.2.2. Subject identification

When inclusion is performed subjects will be assigned a subject identification code (subject number) which will ensure unambiguous identification throughout the study.
Subject identification code will be generated as follows: *H18-VV-A-NNN*

H18: mandatory, abbreviated code of the study;
VV: code of the study centre (listed in Annex 1, List of investigators);
A: age group identifier, generated as follows:
- for children aged 3-12 years: 1;
- for adolescents aged 13-17 years: 2;
- for non-elderly adults aged 18-65 years: 3;
- for elderly subjects aged over 65 years: 4;

NNN: serial number per age group, starting from 001 in each age group.

9.2.3. Follow up

Patient follow-up will be performed seven (7) days after vaccination by phone contact with respect to defined AEIs and other AEs following vaccination. All AEs will be recorded on Data Report Forms regarding to occurrence and severity.

A clear concise reason should be recorded in the Data Report Form for subjects ending the study prematurely. All study data from withdrawals should be retained.

9.3. Variables

The occurrence rates of AEIs as reactogenicity endpoints as well as other reported AEs will be evaluated. The following AEIs (i.e. reactogenicity endpoints) are defined:

- Vaccinaton site pain
- Vaccination site erythema
- Vaccination site swelling
- Vaccination site induration
- Vaccination site haematoma
- Urticaria
- Erythema
- Headache

- Fever
- Malaise
- Chills
- Fatigue
- Hyperhidrosis
- Pallor
- Dizziness
- Numbness
- Dysphonia
- Nausea
- Myalgia
- Arthralgia
- Pain in extremity
- Hypersensitivity reactions, including ocular symptoms
- Use of medicines available without prescription to treat pain and fever

9.4. Data sources

Data Report Forms will be available for data recording. However, source data will be available to document the existence of the subject and substantiate integrity of study data collected.

9.5. Study size

The sample size was determined in accordance with the provisions of guide *Interim guidance on enhanced safety surveillance for seasonal influenza vaccines in the EU* stating that a total of at least one hundred (100) male and female vaccinated subjects in each defined age groups should be evaluated. Based on the experience of the study of the previous year (i.e. Study FluvalAB-H-17), age groups defined for children (i.e. children aged 3-5 years and 6-12 years) are aggregated (i.e. children aged 3-12 years). Higher number of adults (aged 18-65 years) and elders (aged over 65 years) are specified in order to reach planned size of the study based on the guidance and the protocol of Study FluvalAB-H-17.

Further, considering approximately ~20% of drop-out, a maximum of six hundred (600) and a minimum of five hundred (500) male and female subjects will be vaccinated with 3Fluart vaccine containing influenza virus strains recommended for the 2015/2016 seasonal epidemics in accordance with the SmPC and involved into the study as between the following planned numbers by age groups:

- Children aged 3-12 years: hundred (100) – hundred and twenty (120) subjects;
- Adolescents aged 13-17 years: hundred (100) – hundred and twenty (120) subjects;
- Adults aged 18-65 years: hundred and fifty (150) – hundred and eighty (180) subjects;
- Elders aged over 65 years: hundred and fifty (150) – hundred and eighty (180) subjects.

9.6. Data management

During the course of this study, investigators will record AEs by telephone follow up. Data collected on each study subject will be recorded on Data Report Forms. The investigator is responsible for ensuring that all sections of each Data Report Form are completed correctly, and that entries can be verified against source data. The study monitor will review the Data Report Forms, will check them compared to the source data, for completeness and conformity. Control checks on the data included in the database will be performed at the end of the study. Clean data sets will be provided for statistical analysis and reporting.

Data Report Forms are expected to ensure awareness of the sponsor of the occurrence and severity of defined AEIs and other AEs. Further processing of the recorded events (including further data collection and follow-up) will be performed throughout the routine Pharmacovigilance procedures of the manufacturer of 3Fluart suspension for injection, outside the scope of this study.

9.7. Data analysis

All AEs of the study will be coded using the latest approved version of MedDRA. The occurrence rates of defined AEIs and AEs will be stratified per age groups and gender; summarized by System Organ Class (SOC) and Preferred Term (PT); related events (i.e. ARs) will be compared to that expected for 3Fluart vaccine, in order to evaluate the potential for an increased risk related to vaccination therewith, than already known.

All individual data will be listed. Every subject who has already been vaccinated and involved in the study will be included in the statistical analysis. Descriptive and comparative statistics will be used. The assessment will be based on the following considerations:

- Evaluation of the occurrence of AEIs and other AEs in vaccinated subjects participating in the study. Occurrence rate of each AE will be presented by age group and severity.
- Rapid detection of any clinically significant change compared to what was known or expected with the previous vaccine compositions in the frequency and severity of ARs in vaccinated subjects participating in the study. Comparison will be performed between ARs of the study and ARs observed in the last clinical trial performed with 3Fluart influenza vaccine; further, between ARs of the study and with those defined in the SmPC of 3Fluart influenza vaccine.

9.8. Quality control

The study monitor will review Data Report Forms and check them compared to the source data, for completeness and conformity. Fluart Innovative Vaccines Ltd., as the sponsor of this study, is responsible for assuring proper study conduct in regard to protocol adherence and validity of the data recorded on the Data Report Forms. Fluart Innovative Vaccines Ltd. shall assign a study monitor to this study. His/her duties are to assist the investigator in the maintenance of complete, legible, well-organized, and easily retrievable data. In addition, the monitor will ensure that the investigator understands all applicable regulations concerning the study. The investigator agrees to allow the monitor direct access to all study data of the study subjects for the above purposes and agrees to assist the monitor in these activities. The investigator accepts that the monitor will visit the clinic to review and verify the data

collected. The monitor will regard all information that is supplied to him or her as strictly confidential.

9.9. Limitations of the research methods

A potential limitation of the research method is the average low number of children and adolescents vaccinated with seasonal influenza vaccines in Hungary.

9.10. Other aspects

Not applicable.

10. PROTECTION OF HUMAN SUBJECTS

The study will be conducted with the approval of National Institute of Pharmacy and Nutrition, Hungary (i.e. OGYÉI) and of Ethics Committee, Hungary (i.e. ETT-TUKEB).

Each subject will be identified by subject identification codes (subject numbers) after having entered the study which will ensure unambiguous identification throughout the study. Codes will not contain any personal data or data contributing to the identification of participants.

In the conduct of the study, ethical principles laid down in *Declaration of Helsinki* will be followed.

Further, all information gathered during the conduct of the study will be managed in terms of privacy in line with provisions of Hungarian laws (i.e. *1997. évi XLVII. törvény az egészségügyi és a hozzájuk kapcsolódó személyes adatok kezeléséről és védelméről* and *2011. évi CXII. törvény az információs önrendelkezési jogról és az információszabadságról*).

11. MANAGEMENT AND REPORTING OF ADVERSE EVENTS / ADVERSE REACTIONS

Data Report Forms are expected to ensure awareness of the sponsor of the occurrence and severity of defined AEIs and other AEs.

Further processing of the recorded events (including further data collection and follow-up) will be performed throughout the routine Pharmacovigilance procedures of Fluart Innovative Vaccines Ltd., outside the scope of this study.

Definition of Adverse Events (AEs)

An Adverse Event (AE) is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product, and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product. This definition includes any occurrence that is new in onset, aggravated/deteriorated in severity or frequency from the baseline condition.

Abnormal results of diagnostic procedures including laboratory test abnormalities are considered AEs if they:

- result in discontinuation from the trial;
- require treatment or any other therapeutic intervention;
- require further diagnostic evaluation (excluding a repetition of the same procedure to confirm the abnormality);
- are associated with clinical signs or symptoms judged by the investigator to have a significant clinical relevance.

Definition of Adverse Events of Interest (AEIs)

Adverse Events of Interest (AEIs) are the following predefined reactogenicity endpoints of the study: vaccination site pain, vaccination site erythema, vaccination site swelling, vaccination site induration, vaccination site haematoma, urticaria, erythema, headache, fever, malaise, chills, fatigue, hyperhidrosis, pallor, dizziness, numbness, dysphonia, nausea, myalgia, arthralgia, pain in extremity (defined in accordance with the SmPC of 3Fluart influenza vaccine), hypersensitivity reactions, including ocular symptoms and use of medicines available without prescription to treat pain and fever (further, defined in accordance with *EMA/PRAC/135943/2014 part 2.4.1*.).

Definition for the assessment of severity

- Mild: transient or mild discomfort; no limitation in activity; no medical intervention/therapy required.
- Moderate: mild to moderate limitation in activity; some assistance may be needed; no or minimal medical intervention/therapy required.
- Severe: marked limitation in activity; some assistance usually required; medical intervention/therapy required, hospitalization possible.

- Life threatening: extreme limitation in activity; significant assistance required; significant medical intervention/therapy required, hospitalization or hospice care probable.

It is to be noted that in case of AEI "use of medicines available without prescription to treat pain and fever" definition of severity refers to the severity of pain and fever of which treatment medicines without prescription are applied.

Definition of age groups

Subgroups are defined according to age groups, as follows:

- Children aged between 3-12 years: A patient is belonging to age group of 3-12 years, if he/she has already been turning 3, but has not yet been turning 13 on the day of enrolment.
- Adolescents aged between 13-17 years: A patient is belonging to age group of 13-17 years, if he/she has already been turning 13, but has not yet been turning 18 on the day of enrolment.
- Adults aged between 18-65 years: A patient is belonging to age group 18-65 years, if he/she has already been turning 18, but has not yet been turning 66 on the day of enrolment.
- Elders aged over 65 years: A patient is belonging to age group over 65 years, if he/she has already been turning 66 on the day of enrolment.

12. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

Information concerning the study drug, patient applications, processes, unpublished scientific data and other pertinent information is confidential and remain the property of Fluart Innovative Vaccines Ltd. Details should be disclosed only to the persons involved in the approval or conduct of the study. The investigator may use this information for the purpose of the study only. It is understood by the investigator that the company will use the information obtained during the study in connection with the development of the vaccine and therefore may disclose it as required to other investigators or to regulatory agencies. In order to allow for the use of the information derived from this study, the investigator understands that he has an obligation to provide the sponsor with all data obtained during the study.

Information of defined AEIs and other AEs regarding to occurrence and severity will be reported weekly for all weeks of follow up to the National Institute of Pharmacy and Nutrition, Hungary (i.e. OGYÉI). Data will be summarized in Expedited Summary Safety Report and further in Final Study Report.

Data contained in the Weekly Summary Safety Reports and in the Expedited Summary Safety Report will be presented according to the description on the format and content of *Interim guidance on enhanced safety surveillance for seasonal influenza vaccines in the EU' (EMA/PRAC/222346/2014)*. Final Study Report will be presented according to the provisions of *Guidance for the format and content of the final study report of non-interventional post-authorization safety studies (EMA/48663/2013)*.

Further, the study registration is to be performed in EU PAS Register of which data will be continuously updated by the Coordinating investigator with regard to current study status and new information.

Reporting of AEs to the competent authorities will be performed in accordance with the Hungarian and European Union legislation of reporting in spontaneous environment.

13. REFERENCES

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3. *2011. évi CXII. törvény az információs önrendelkezési jogról és az információszabadságról*
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5. *52/2005. (XI. 18) EüM rendelet* – az emberi alkalmazásra kerülő gyógyszerek forgalomba hozataláról
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7. *Council Regulation (EEC) 2309/93* – laying down Community procedures for the authorization and supervision of medicinal products for human and veterinary use and establishing a European Agency for the Evaluation of Medicinal Products. Amended by Commission Regulation (EC) 649/98, amending the Annex to Council Regulation (EEC) No 2309/93. The Council of the European Communities. 1993 July
8. EMEA/359381/2009 (2009). *CHMP Recommendations for the Pharmacovigilance Plan as part of the Risk Management Plan to be submitted with the Marketing Authorisation Application for a Pandemic Influenza Vaccine.* European Medicines Agency, EMA. 2009, September
9. EMA/PRAC/222346/2014 (2014). *Interim guidance on enhanced safety surveillance for seasonal influenza vaccines in the EU*. European Medicines Agency, EMA. 2014 April
10. EMA/488220/2012 (2013). *Guideline on good pharmacovigilance practices (GVP). Product. or Population-Specific Considerations I: Vaccines for prophylaxis against infectious diseases.* European Medicines Agency, EMA. 2013 December
11. EMA/813938/2011 Rev 1 (2013). *Guideline on good pharmacovigilance practices (GVP) Module VIII. Post- authorization safety studies (Rev 1).* European Medicines Agency, EMA. 2013 April
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14. WMA. (2013). *WMA Declaration of Helsinki - Ethical Principles for Medical Research Involving Human Subjects.* 64th WMA General Assembly, Fortaleza, Brazil, October 2013.

ANNEX 1. LIST OF STAND-ALONE DOCUMENTS

Number	Doc. Ref. No.	Date	Title[1]
1.	List of investigators v01	06 July 2015	List of investigators
2.	3Fluart-H-18 Data Report Form v03	07 October 2015	Data Report Form
3.	3Fluart-H-18 Patient Information for patients aged 3-6 years v01	07 October 2015	Patient Information
4.	3Fluart-H-18 Patient Information for patients aged 7-15 years v02	07 October 2015	Patient Information
5.	3Fluart-H-18 Patient Information for patients aged 16-17 years v02	07 October 2015	Patient Information
6.	3Fluart-H-18 Patient Information for legal representatives v02	07 October 2015	Patient Information
7.	3Fluart-H-18 Patient Information for patients aged over 18 years v02	07 October 2015	Patient Information
8.	3Fluart-H-18 Informed Consent for patients aged 3-6 years v01	07 October 2015	Informed Consent
9.	3Fluart-H-18 Informed Consent for patients aged 7-15 years v02	07 October 2015	Informed Consent
10.	3Fluart-H-18 Informed Consent for patients aged 16-17 years v02	07 October 2015	Informed Consent
11.	3Fluart-H-18 Informed Consent for legal representatives v02	07 October 2015	Informed Consent
12.	3Fluart-H-18 Informed Consent for patients aged over 18 years v02	07 October 2015	Informed Consent

[1] Documents are not incorporated into the text, are maintained separately from the study protocol.

ANNEX 2. ENCePP CHECKLIST FOR STUDY PROTOCOLS

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Doc.Ref. EMA/540136/2009

European Network of Centres for Pharmacoepidemiology and Pharmacovigilance

ENCePP Checklist for Study Protocols (Revision 2, amended)

Adopted by the ENCePP Steering Group on 14/01/2013

The European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) welcomes innovative designs and new methods of research. This Checklist has been developed by ENCePP to stimulate consideration of important principles when designing and writing a pharmacoepidemiological or pharmacovigilance study protocol. The Checklist is intended to promote the quality of such studies, not their uniformity. The user is also referred to the ENCePP Guide on Methodological Standards in Pharmacoepidemiology which reviews and gives direct electronic access to guidance for research in pharmacoepidemiology and pharmacovigilance.

For each question of the Checklist, the investigator should indicate whether or not it has been addressed in the study protocol. If the answer is "Yes", the page number(s) of the protocol where this issue has been discussed should be specified. It is possible that some questions do not apply to a particular study (for example in the case of an innovative study design). In this case, the answer 'N/A' (Not Applicable) can be checked and the "Comments" field included for each section should be used to explain why. The "Comments" field can also be used to elaborate on a "No" answer.

This Checklist should be included as an Annex by marketing authorisation holders when submitting the protocol of a non-interventional post-authorisation safety study (PASS) to a regulatory authority (see the Guidance on the format and content of the protocol of non-interventional post-authorisation safety studies). Note, the Checklist is a supporting document and does not replace the format of the protocol for PASS as recommended in the Guidance and Module VIII of the Good pharmacovigilance practices (GVP).

Study title:
Prospective non-interventional cohort study to assess safety and tolerability of 3Fluart 2015/2016 trivalent seasonal influenza vaccine in children, adolescents, adults and elderly subjects

Study reference number:
3Fluart-H-18

Section 1: Milestones	Yes	No	N/A	Page Number(s)
1.1 Does the protocol specify timelines for				
1.1.1 Start of data collection[1]	☒	☐	☐	13, 15
1.1.2 End of data collection[2]	☒	☐	☐	13, 15
1.1.3 Study progress report(s)	☒	☐	☐	12, 21
1.1.4 Interim progress report(s)	☒	☐	☐	13, 15
1.1.5 Registration in the EU PAS register	☒	☐	☐	1
1.1.6 Final report of study results.	☒	☐	☐	26

Comments:
None.

[1] Date from which information on the first study is first recorded in the study dataset or, in the case of secondary use of data, the date from which data extraction starts.
[2] Date from which the analytical dataset is completely available.

ENCePP Checklist for Study Protocols (Revision 2)

Section 2: Research question	Yes	No	N/A	Page Number(s)
2.1 Does the formulation of the research question and objectives clearly explain:				
2.1.1 Why the study is conducted? (e.g. to address an important public health concern, a risk identified in the risk management plan, an emerging safety issue)	☒	☐	☐	8, 16
2.1.2 The objective(s) of the study?	☒	☐	☐	9, 17
2.1.3 The target population? (i.e. population or subgroup to whom the study results are intended to be generalised)	☒	☐	☐	10, 18
2.1.4 Which formal hypothesis(-es) is (are) to be tested?	☐	☐	☒	
2.1.5 If applicable, that there is no *a priori* hypothesis?	☐	☐	☒	

Comments:
None.

Section 3: Study design	Yes	No	N/A	Page Number(s)
3.1 Is the study design described? (e.g. cohort, case-control, randomised controlled trial, new or alternative design)	☒	☐	☐	18
3.2 Does the protocol specify the primary and secondary (if applicable) endpoint(s) to be investigated?	☒	☐	☐	9, 17
3.3 Does the protocol describe the measure(s) of effect? (e.g. relative risk, odds ratio, deaths per 1000 person-years, absolute risk, excess risk, incidence rate ratio, hazard ratio, number needed to harm (NNH) per year)	☒	☐	☐	21

Comments:
None.

Section 4: Source and study populations	Yes	No	N/A	Page Number(s)
4.1 Is the source population described?	☒	☐	☐	10, 18
4.2 Is the planned study population defined in terms of:				
4.2.1 Study time period?	☒	☐	☐	13, 16
4.2.2 Age and sex?	☒	☐	☐	10, 18
4.2.3 Country of origin?	☐	☐	☒	2, 18
4.2.4 Disease/indication?	☒	☐	☐	1, 39
4.2.5 Co-morbidity?	☒	☐	☐	40
4.2.6 Seasonality?	☒	☐	☐	39
4.3 Does the protocol define how the study population will be sampled from the source population? (e.g. event or inclusion/exclusion criteria)	☒	☐	☐	18

Comments:
None.

Section 5: Exposure definition and measurement	Yes	No	N/A	Page Number(s)
5.1 Does the protocol describe how exposure is defined and measured? (e.g. operational details for defining and categorising exposure)	☒	☐	☐	18, 19, 20
5.2 Does the protocol discuss the validity of exposure measurement? (e.g. precision, accuracy, prospective				

Section 5: Exposure definition and measurement	Yes	No	N/A	Page Number(s)
ascertainment, exposure information recorded before the outcome occurred, use of validation sub-study)	☐	☐	☒	
5.3 Is exposure classified according to time windows? (e.g. current user, former user, non-use)	☒	☐	☐	18
5.4 Is exposure classified based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	☐	☐	☒	
5.5 Does the protocol specify whether a dose-dependent or duration-dependent response is measured?	☐	☐	☒	

Comments:

Biological mechanism of action, pharmacokinetics, pharmacodynamics of the drug, dose-dependent and duration dependent response are not addressed.

Section 6: Endpoint definition and measurement	Yes	No	N/A	Page Number(s)
6.1 Does the protocol describe how the endpoints are defined and measured?	☒	☐	☐	10, 18
6.2 Does the protocol discuss the validity of endpoint measurement? (e.g. precision, accuracy, sensitivity, specificity, positive predictive value, prospective or retrospective ascertainment, use of validation sub-study)	☐	☐	☒	

Comments:

None.

Section 7: Confounders and effect modifiers	Yes	No	N/A	Page Number(s)
7.1 Does the protocol address known confounders? (e.g. collection of data on known confounders, methods of controlling for known confounders)	☐	☐	☒	
7.2 Does the protocol address known effect modifiers? (e.g. collection of data on known effect modifiers, anticipated direction of effect)	☐	☐	☒	

Comments:

None.

Section 8: Data sources	Yes	No	N/A	Page Number(s)
8.1 Does the protocol describe the data source(s) used in the study for the ascertainment of:				
8.1.1 Exposure? (e.g. pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview, etc.)	☒	☐	☐	19
8.1.2 Endpoints? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics, etc.)	☒	☐	☐	10, 18
8.1.3 Covariates?	☒	☐	☐	9, 17
8.2 Does the protocol describe the information available from the data source(s) on:				
8.2.1 Exposure? (e.g. date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)	☒	☐	☐	16
8.2.2 Endpoints? (e.g. date of occurrence, multiple event, severity measures related to event)	☒	☐	☐	10, 18
8.2.3 Covariates? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, life style, etc.)	☒	☐	☐	10, 19

Section 8: Data sources	Yes	No	N/A	Page Number(s)
8.3 Is a coding system described for:				
8.3.1 Diseases? (e.g. International Classification of Diseases (ICD)-10)	☐	☐	☒	
8.3.2 Endpoints? (e.g. Medical Dictionary for Regulatory Activities (MedDRA) for adverse events)	☒	☐	☐	12, 21
8.3.3 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC)Classification System)	☒	☐	☐	1, 39
8.4 Is the linkage method between data sources described? (e.g. based on a unique identifier or other)	☒	☐	☐	19

Comments:
None.

Section 9: Study size and power	Yes	No	N/A	Page Number(s)
9.1 Is sample size and/or statistical power calculated?	☒	☐	☐	20

Comments:
None.

Section 10: Analysis plan	Yes	No	N/A	Page Number(s)
10.1 Does the plan include measurement of excess risks?	☒	☐	☐	21, 23
10.2 Is the choice of statistical techniques described?	☒	☐	☐	21
10.3 Are descriptive analyses included?	☒	☐	☐	21
10.4 Are stratified analyses included?	☒	☐	☐	21
10.5 Does the plan describe methods for adjusting for confounding?	☐	☐	☒	
10.6 Does the plan describe methods addressing effect modification?	☐	☐	☒	

Comments:
None.

Section 11: Data management and quality control	Yes	No	N/A	Page Number(s)
11.1 Is information provided on the management of missing data?	☒	☐	☐	21
11.2 Does the protocol provide information on data storage? (e.g. software and IT environment, database maintenance and anti-fraud protection, archiving)	☒	☐	☐	21, 26
11.3 Are methods of quality assurance described?	☒	☐	☐	21
11.4 Does the protocol describe possible quality issues related to the data source(s)?	☒	☐	☐	21
11.5 Is there a system in place for independent review of study results?	☒	☐	☐	18, 21

Comments:
None.

Section 12: Limitations	Yes	No	N/A	Page Number(s)
12.1 Does the protocol discuss: 12.1.1 Selection biases? 12.1.2 Information biases? (e.g. anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods)	☐ ☐	☐ ☐	☒ ☒	
12.2 Does the protocol discuss study feasibility? (e.g. sample size, anticipated exposure, duration of follow-up in a cohort study, patient recruitment)	☒	☐	☐	19
12.3 Does the protocol address other limitations?	☒	☐	☐	23

Comments:
None.

Section 13: Ethical issues	Yes	No	N/A	Page Number(s)
13.1 Have requirements of Ethics Committee/Institutional Review Board approval been described?	☒	☐	☐	23, 25
13.2 Has any outcome of an ethical review procedure been addressed?	☒	☐	☐	23
13.3 Have data protection requirements been described?	☒	☐	☐	23

Comments:
None.

Section 14: Amendments and deviations	Yes	No	N/A	Page Number(s)
14.1 Does the protocol include a section to document future amendments and deviations?	☒	☐	☐	15

Comments:
None.

Section 15: Plans for communication of study results	Yes	No	N/A	Page Number(s)
15.1 Are plans described for communicating study results (e.g. to regulatory authorities)?	☒	☐	☐	23, 25
15.2 Are plans described for disseminating study results externally, including publication?	☒	☐	☐	26

Comments:
None.

Name of the main author of the protocol: DR SOLYA CZUCZAI PHARMD

Date: 7/10/2015

Signature: 

ANNEX 3. ADDITIONAL INFORMATION

ANNEX 3.1 Declaration of Helsinki

WMA Declaration of Helsinki - Ethical Principles for Medical Research Involving Human Subjects

Adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964
and amended by the:
29th WMA General Assembly, Tokyo, Japan, October 1975
35th WMA General Assembly, Venice, Italy, October 1983
41st WMA General Assembly, Hong Kong, September 1989
48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996
52nd WMA General Assembly, Edinburgh, Scotland, October 2000
53rd WMA General Assembly, Washington DC, USA, October 2002 (Note of Clarification added)
55th WMA General Assembly, Tokyo, Japan, October 2004 (Note of Clarification added)
59th WMA General Assembly, Seoul, Republic of Korea, October 2008
64th WMA General Assembly, Fortaleza, Brazil, October 2013

Preamble

1. The World Medical Association (WMA) has developed the Declaration of Helsinki as a statement of ethical principles for medical research involving human subjects, including research on identifiable human material and data.

The Declaration is intended to be read as a whole and each of its constituent paragraphs should be applied with consideration of all other relevant paragraphs.

2. Consistent with the mandate of the WMA, the Declaration is addressed primarily to physicians. The WMA encourages others who are involved in medical research involving human subjects to adopt these principles.

General Principles

3. The Declaration of Geneva of the WMA binds the physician with the words, "The health of my patient will be my first consideration," and the International Code of Medical Ethics declares that, "A physician shall act in the patient's best interest when providing medical care."

4. It is the duty of the physician to promote and safeguard the health, well-being and rights of patients, including those who are involved in medical research. The physician's knowledge and conscience are dedicated to the fulfilment of this duty.

5. Medical progress is based on research that ultimately must include studies involving human subjects.

6. The primary purpose of medical research involving human subjects is to understand the causes, development and effects of diseases and improve preventive, diagnostic and therapeutic interventions (methods, procedures and treatments). Even the best proven interventions must be evaluated continually through research for their safety, effectiveness, efficiency, accessibility and quality.

7. Medical research is subject to ethical standards that promote and ensure respect for all human subjects and protect their health and rights.

8. While the primary purpose of medical research is to generate new knowledge, this goal can never take precedence over the rights and interests of individual research subjects.

9. It is the duty of physicians who are involved in medical research to protect the life, health, dignity, integrity, right to self-determination, privacy, and confidentiality of personal information of research subjects. The responsibility for the protection of research subjects must always rest with the physician or other health care professionals and never with the research subjects, even though they have given consent.

10. Physicians must consider the ethical, legal and regulatory norms and standards for research involving human subjects in their own countries as well as applicable international norms and standards. No national or international ethical, legal or regulatory requirement should reduce or eliminate any of the protections for research subjects set forth in this Declaration.

11. Medical research should be conducted in a manner that minimises possible harm to the environment.

12. Medical research involving human subjects must be conducted only by individuals with the appropriate ethics and scientific education, training and qualifications. Research on patients or healthy volunteers requires the supervision of a competent and appropriately qualified physician or other health care professional.

13. Groups that are underrepresented in medical research should be provided appropriate access to participation in research.

14. Physicians who combine medical research with medical care should involve their patients in research only to the extent that this is justified by its potential preventive, diagnostic or therapeutic value and if the physician has good reason to believe that participation in the research study will not adversely affect the health of the patients who serve as research subjects.

15. Appropriate compensation and treatment for subjects who are harmed as a result of participating in research must be ensured.

Risks, Burdens and Benefits

16. In medical practice and in medical research, most interventions involve risks and burdens.

Medical research involving human subjects may only be conducted if the importance of the objective outweighs the risks and burdens to the research subjects.

17. All medical research involving human subjects must be preceded by careful assessment of predictable risks and burdens to the individuals and groups involved in the research in comparison with foreseeable benefits to them and to other individuals or groups affected by the condition under investigation.

Measures to minimise the risks must be implemented. The risks must be continuously monitored, assessed and documented by the researcher.

18. Physicians may not be involved in a research study involving human subjects unless they are confident that the risks have been adequately assessed and can be satisfactorily managed.

When the risks are found to outweigh the potential benefits or when there is conclusive proof of definitive outcomes, physicians must assess whether to continue, modify or immediately stop the study.

Vulnerable Groups and Individuals

19. Some groups and individuals are particularly vulnerable and may have an increased likelihood of being wronged or of incurring additional harm.

All vulnerable groups and individuals should receive specifically considered protection.

20. Medical research with a vulnerable group is only justified if the research is responsive to the health needs or priorities of this group and the research cannot be carried out in a non-vulnerable group. In addition, this group should stand to benefit from the knowledge, practices or interventions that result from the research.

Scientific Requirements and Research Protocols

21. Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and adequate laboratory and, as appropriate, animal experimentation. The welfare of animals used for research must be respected.

22. The design and performance of each research study involving human subjects must be clearly described and justified in a research protocol.

The protocol should contain a statement of the ethical considerations involved and should indicate how the principles in this Declaration have been addressed. The protocol should include information regarding funding, sponsors, institutional affiliations, potential conflicts of interest, incentives for subjects and information regarding provisions for treating and/or compensating subjects who are harmed as a consequence of participation in the research study.

In clinical trials, the protocol must also describe appropriate arrangements for post-trial provisions.

Research Ethics Committees

23. The research protocol must be submitted for consideration, comment, guidance and approval to the concerned research ethics committee before the study begins. This committee must be transparent in its functioning, must be independent of the researcher, the sponsor and any other undue influence and must be duly qualified. It must take into consideration the laws and regulations of the country or countries in which the research is to be performed as well as applicable international norms and standards but these must not be allowed to reduce or eliminate any of the protections for research subjects set forth in this Declaration.

The committee must have the right to monitor ongoing studies. The researcher must provide monitoring information to the committee, especially information about any serious adverse events. No amendment to the protocol may be made without consideration and approval by the committee. After the end of the study, the researchers must submit a final report to the committee containing a summary of the study's findings and conclusions.

Privacy and Confidentiality

24. Every precaution must be taken to protect the privacy of research subjects and the confidentiality of their personal information.

Informed Consent

25. Participation by individuals capable of giving informed consent as subjects in medical research must be voluntary. Although it may be appropriate to consult family members or community leaders, no individual capable of giving informed consent may be enrolled in a research study unless he or she freely agrees.

26. In medical research involving human subjects capable of giving informed consent, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail, post-study provisions and any other relevant aspects of the study. The potential subject must be informed of the right to refuse to participate in the study or to withdraw consent to participate at any time

without reprisal. Special attention should be given to the specific information needs of individual potential subjects as well as to the methods used to deliver the information.

After ensuring that the potential subject has understood the information, the physician or another appropriately qualified individual must then seek the potential subject's freely-given informed consent, preferably in writing. If the consent cannot be expressed in writing, the non-written consent must be formally documented and witnessed.

All medical research subjects should be given the option of being informed about the general outcome and results of the study.

27. When seeking informed consent for participation in a research study the physician must be particularly cautious if the potential subject is in a dependent relationship with the physician or may consent under duress. In such situations the informed consent must be sought by an appropriately qualified individual who is completely independent of this relationship.

28. For a potential research subject who is incapable of giving informed consent, the physician must seek informed consent from the legally authorised representative. These individuals must not be included in a research study that has no likelihood of benefit for them unless it is intended to promote the health of the group represented by the potential subject, the research cannot instead be performed with persons capable of providing informed consent, and the research entails only minimal risk and minimal burden.

29. When a potential research subject who is deemed incapable of giving informed consent is able to give assent to decisions about participation in research, the physician must seek that assent in addition to the consent of the legally authorised representative. The potential subject's dissent should be respected.

30. Research involving subjects who are physically or mentally incapable of giving consent, for example, unconscious patients, may be done only if the physical or mental condition that prevents giving informed consent is a necessary characteristic of the research group. In such circumstances the physician must seek informed consent from the legally authorised representative. If no such representative is available and if the research cannot be delayed, the study may proceed without informed consent provided that the specific reasons for involving subjects with a condition that renders them unable to give informed consent have been stated in the research protocol and the study has been approved by a research ethics committee. Consent to remain in the research must be obtained as soon as possible from the subject or a legally authorised representative.

31. The physician must fully inform the patient which aspects of their care are related to the research. The refusal of a patient to participate in a study or the patient's decision to withdraw from the study must never adversely affect the patient-physician relationship.

32. For medical research using identifiable human material or data, such as research on material or data contained in biobanks or similar repositories, physicians must seek informed consent for its collection, storage and/or reuse. There may be exceptional situations where consent would be impossible or impracticable to obtain for such research. In such situations the research may be done only after consideration and approval of a research ethics committee.

Use of Placebo

33. The benefits, risks, burdens and effectiveness of a new intervention must be tested against those of the best proven intervention(s), except in the following circumstances:

Where no proven intervention exists, the use of placebo, or no intervention, is acceptable; or

Where for compelling and scientifically sound methodological reasons the use of any intervention less effective than the best proven one, the use of placebo, or no intervention is necessary to determine the efficacy or safety of an intervention

and the patients who receive any intervention less effective than the best proven one, placebo, or no intervention will not be subject to additional risks of serious or irreversible harm as a result of not receiving the best proven intervention.

Extreme care must be taken to avoid abuse of this option.

Post-Trial Provisions

34. In advance of a clinical trial, sponsors, researchers and host country governments should make provisions for post-trial access for all participants who still need an intervention identified as beneficial in the trial. This information must also be disclosed to participants during the informed consent process.

Research Registration and Publication and Dissemination of Results

35. Every research study involving human subjects must be registered in a publicly accessible database before recruitment of the first subject.

36. Researchers, authors, sponsors, editors and publishers all have ethical obligations with regard to the publication and dissemination of the results of research. Researchers have a duty to make publicly available the results of their research on human subjects and are accountable for the completeness and accuracy of their reports. All parties should adhere to accepted guidelines for ethical reporting. Negative and inconclusive as well as positive results must be published or otherwise made publicly available. Sources of funding, institutional affiliations and conflicts of interest must be declared in the publication. Reports of research not in accordance with the principles of this Declaration should not be accepted for publication.

Unproven Interventions in Clinical Practice

37. In the treatment of an individual patient, where proven interventions do not exist or other known interventions have been ineffective, the physician, after seeking expert advice, with informed consent from the patient or a legally authorised representative, may use an unproven intervention if in the physician's judgement it offers hope of saving life, re-establishing health or alleviating suffering. This intervention should subsequently be made the object of research, designed to evaluate its safety and efficacy. In all cases, new information must be recorded and, where appropriate, made publicly available.