CLINICAL STUDY COLLABORATION AGREEMENT

1. PARTIES

Hospital District of Helsinki and Uusimaa/Helsinki University Hospital, Neurocenter, Department of Neurology
Business ID/VAT: FI 1567535-0
Address of Center: Haartmaninkatu 4, P.O. Box 340, FI-00029 HUS, Finland (hereinafter the "Coordinating Center")
Lead Principal Investigator (hereinafter "Lead-PI"): [redacted]
Tel: [redacted]
[redacted]
[redacted]

Your institution: FUNDACIÓN PÚBLICA ANDALUZA PARA LA INVESTIGACIÓN BIOSANITARIA DE ANDALUCÍA ORIENTAL-ALEJANDRO OTERO
Business ID/VAT: G-18374199
Address: Avenida de Madrid , 15. 2ª planta, 18012,Granada, España (hereinafter the "Site")
Site Principal Investigator: XXX [redacted] (hereinafter the "Site-PI")
Email: [redacted]

2. SCOPE OF THE AGREEMENT

Under this agreement the parties agree to conduct a clinical study as defined in the Protocol in Appendix I, named Searching for Explanations for Cryptogenic Stroke in the Young: Revealing the Etiology, Triggers, and Outcome (SECRETO), (hereinafter the "Study", protocol version 3.0, NCT01934725, Lead-PI [redacted]) as may be amended from time to time. A considerable proportion of young patients (aged below 50) with ischemic stroke remain without a definitive cause for their strokes (i.e. cryptogenic stroke). Limited data exist on the underlying mechanisms of such events and long-term prognosis of this patient population. Such information would be essential, for instance, for developing primary and secondary prevention measures.

In addition to well-known cardiac interatrial abnormalities, such as patent foramen ovale and atrial septal aneurysm, even subtle cardiac structural or functional abnormalities may play a role in cryptogenic stroke and be linked to risk of recurrent events. In order to produce high-quality standardized cardiac structural and functional data in a multicenter study, a step-by-step echocardiography performance protocol have been developed. The echocardiography data will be centrally analyzed. Therefore, only dedicated site cardiologist(s) or clinical physiologist(s) familiar with the protocol should perform echocardiography examinations for subjects recruited in the Study.

Due to the relative rarity of the studied event the Study is conducted as a multicenter international collaboration in order to facilitate timely recruitment and patient follow-up. This network of investigators forms the "Study Consortium". The Study is set up and organized by the Clinical Stroke Research Center, Department of Neurology, Helsinki University Hospital, and led by the Lead-PI (Chief Investigator). A team involving Study co-PIs, Country Coordinators, Substudy PIs, and site-PIs (hereinafter the "Executive Committee") will be responsible, in close collaboration with the Coordinating Center, for practical management of the Study, making decisions on use of the database and samples, creating an analysis plan, and deciding on publications. An invited board of scientists covering expertise on key fields in the Study (hereinafter the "Scientific Committee") will be guiding with scientific framework of the Study, details of the protocol, data to be collected, sample analysis plan, and publication policy.

3. PURPOSE OF THE AGREEMENT

The purpose of this agreement is to agree on terms and conditions, as well as procedures, according to which the Study will be conducted, and on the division of duties and responsibilities between the parties conducting the Study.

4. SCHEDULE AND COURSE OF THE STUDY

An initial favorable opinion by the Coordinating Ethics Committee of the Hospital District of Helsinki and Uusimaa has been received on 09 Apr 2013 and the conduct of the Study has been approved by Helsinki University Hospital. In addition, appropriate permissions for conducting the study at the Site, if so regulated, shall be obtained prior to the initiation of the Study. The first patient was recruited in Nov 2013 at the Coordinating Center for a pilot phase.

The aim is to enroll 10-15 patients and the corresponding amount of control subjects at the Site. The follow-up period of study patients is 10 years. The global aim is to enroll 600 patients and 600 stroke-free control subjects in the Study. The Coordinating Center is entitled to suspend the recruitment of new subjects, when a sufficient amount of subjects have been recruited into the study.

5. LEGISLATION AND GUIDELINES ON CONDUCTING THE STUDY

The following legislation and regulations shall be complied with in the conduct of the Study:

- Valid Finnish and EU legislation, regulations, and guidelines of the authorities, including but not limited to Responsible Conduct of Research and Procedures for Handling Allegations of Misconduct in Finland (the RCR guidelines, “Hyvä tieteellinen käytäntö ja sen loukkausepäilyt Suomessa”),
- Guideline for Good Clinical Practice (ICH GCP);
- The principles of the (World Medical Association) Declaration of Helsinki;
- Standard Operating Procedures (SOPs) given by the Coordinating Center to the Site and the Site-PI; and
- Study site-specific provisions, regulations, and instructions given by the Site to the Coordinating Center.

6. LIABILITIES AND RESPONSIBILITIES OF THE PARTIES

In addition to the other liabilities and responsibilities described in this agreement, the Site shall:

- Follow the procedures regarding the conduct of the Study set forth by Section 5 of this agreement;
- Get fully acquainted with the protocol and all information and documents provided by the Coordinating Center;
- Ensure that qualified and instructed personnel and adequate equipment are available for the Study and that the Study may also in other respects be conducted in safe conditions;
- Allow participation of the investigators and when appropriate/needed also study nurses in investigator meetings arranged by the Coordinating Center;
- Ensure that the investigators are familiar with the details of the protocol and other liabilities and responsibilities defined in this agreement, and that Investigators are committed to act accordingly;
- Conduct the Study in accordance with the protocol as approved by the Ethics Committee including potential approved amendments thereto;
- Immediately notify the Coordinating Center of all necessary amendments to the protocol or any deviations from the protocol.

In addition to the liabilities and responsibilities described in this agreement, the Coordinating Center shall:

- Provide the Site with the necessary background information and study documents concerning the appropriate and safe conduct of the study;
- Provide the Site with the storage media for recording brain and vascular imaging and echocardiography studies, as well as blood sampling material;
- Ensure necessary training and orientation of the investigators and other personnel of the Site involved in the Study in order to conduct the study in accordance with the protocol. The training, meetings, and traveling related to the conduct of the Study shall be separately agreed between the Coordinating Center, the Site, and the investigators;
- Maintain electronic file repository with up-to-date study documents available;
- Maintain electronic Study database;
- Register the study into an open international publication register according to common practice before starting the patient recruitment; as well as
- Inform the Site of the completion of the study.

7. MATERIAL DELIVERED FOR THE STUDY

The Coordinating Center shall be responsible for the costs related to the following material and their delivery to Site by a courier service:

- Storage media (CDs or DVDs) for recording brain and vascular imaging and echocardiography studies, padded envelopes;
- Blood sample tubes, cryovials, cryoboxes, barcode stickers with unique subject identifiers, laminated sample treatment instructions.

8. SHIPMENT OF BLOOD SAMPLES TO CORE SAMPLE REPOSITORY

The Coordinating Center shall be responsible for the costs related to the shipment of preprocessed blood samples from the Site to the Core Sample Repository located at the Institute for Molecular Medicine Finland [FIMM], Biomedicum Helsinki, Finland by a courier service, understanding that the Core Sample Repository is not a registered biobank under the Finnish Biobank Act, and that the samples are to be used for the purposes of the Study during the term of the Study in accordance with Study subject's consent and not for any other purposes. In addition, costs for preprocessing and temporary storage of blood samples will be covered, if needed.

9. FUNDING

The Coordinating Center shall sponsor the Site with 600€ per enrolled patient and 400€ per enrolled control subject (the Coordinating Center shall cover value-added tax according to Art. 44 and Art. 194 of the Council Directive 2006/112/EC of 28 November 2006). The Coordinating Center shall also cover the costs, i.e. 103,70€ for each study subject, for processing and storing the blood samples at the FIBAO. The Site may utilize the Study protocol to apply further funding from local or national sources.

10. CONFIDENTIALITY

Each party shall keep in confidence all trade and professional secrets of the other. The Site shall keep in confidence especially all information related to and accrued in connection with the Study, the Results, documents, and electronic records (hereinafter "Confidential Information"). All documents and electronic records that contain Confidential Information must be stored in a manner that no third party may have access thereto.

In addition, the personnel of a public party (authority) and its subcontractors are bound by the Act on the openness of governmental activities (621/1999), according to which they must keep in confidence information on e.g. trade and professional secrets.

The obligations of confidentiality and any implied by law shall survive the expiry or termination of this Agreement for whatever reason and continue in force for a period set by any mandatory law or regulation or for fifteen (15) years thereafter whichever expires later.

The confidentiality obligation shall not, however, be applied to Confidential Information, which:

a) Was, as evidenced, in the possession of the receiving party prior to receipt of the Confidential Information from the other party;
b) Has been publicly available or has become publicly available through no act or omission by the party or its employee or a consultant or breach of this agreement;
c) The party has received from a third party without any obligation of confidentiality and which has a right to deliver such information to the other party;
d) Is required to be disclosed, but only to the extent required, by any rule, law, regulation or act of any governmental authority or agency, provided, however, that the receiving party shall use reasonable efforts to give the disclosing party sufficient advance notice to permit it to seek a protective or other similar order with respect to the Confidential Information and thereafter the receiving party shall use its best efforts to disclose only the minimum of the Confidential Information required to be disclosed in order to comply;
e) The other party has developed independently without use of the disclosing party's Confidential Information; or
f) Needs to be disclosed to be able to publish the results properly and in accordance with section 13 below.

Any party invoking an exception set forth above has the burden of proof with respect to the existence of such an exception.

Each party shall promptly return to the other party any Confidential Information no longer needed for the purposes of this agreement or if so requested by the other party.

The principles of the Protection Regulation of the European Union ("GDPR") are outlined in the supplementary Annex.

11. STUDY REGISTER AND PERSONAL DATA PROTECTION

A Study sub-register will be created in connection with the Study at each Study site and compiled into one main register maintained by the Coordinating Center. All Study subjects will be coded with Personal Identification Number (PIN) so that personal identifiers will not be transmitted outside of the Study sites. PIN will be used in all study materials sent outside of the Study sites (herein, electrocardiograms and CDs/DVDs containing neuroimaging and echocardiography studies) and in the Study's electronic database. For clarification, PIN does not mean identity number, but is merely a separate coding number.

GDPR (General Data Protection Regulation of the EU) shall be applied to this agreement, in the Study and the Study subjects (Appendix II).

12. DATA AND RESULTS ACCRUED IN CONNECTION WITH THE STUDY

All information, documents, reports, and other results accrued and generated in connection with this Study (hereinafter "Results") are the property of the Study Consortium the use of which the Executive Committee and Coordinating Center shall agree and decide upon. The Site may use the Results in patient care.

Patient records and other data collected by the Site for its own use as well as materials (e.g. human biosamples) remain the property to each Consortium member providing such information or materials.

13. INTELLECTUAL PROPERTY RIGHTS

All copyrights, industrial rights and other intellectual property rights jointly generated as a result of this Study or jointly generated in connection thereto and which are related to the Results are the joint property of the Study Consortium researchers and their respective organizations as follows from the Act on the Right in Employee Inventions, the use of which shall be determined in cooperation with the researcher's respective organizations.

The ownership of jointly generated Results shall rest with the parties generating the Results jointly, each jointly owning party having an undivided interest in that Result and being free to use the Results for its own internal non-commercial purposes as if such party had been the sole owner thereof, subject to obligations of confidentiality towards the other joint owner/s. If needed, the jointly owning parties shall agree separately in writing on the conditions for other uses of the jointly owned Results. No party jointly owning any Results shall do anything, which would prejudice the rights of the other joint owner/s.

The parties not owning the Results shall have a royalty-free user right for research purposes to Results generated by the other parties. Other user rights shall be agreed upon by the respective parties separately in writing. The rights granted in accordance with this paragraph shall apply, provided that the party has fulfilled all other obligations in accordance with this Agreement.

14. PUBLICATION OF RESULTS

Regarding publication of the Study results the following principles shall be followed:

- Publication of the Results jointly borne within the Study Consortium shall be coordinated by the Executive Committee, in guidance of the Scientific Committee;
- Scientific hypotheses generated by the Study investigators during the course of the Study shall be subjected to evaluation by the Scientific Committee, presented to the Executive Committee, and agreed between the Site/investigator and the Executive Committee;
- In case of divergent views between the members of the Executive Committee, a voting will be decisive, and no publication of Results is allowed unless agreed by the Executive Committee with a majority vote;
- The Scientific or Executive Committee members do not have any subjective right to authorship in manuscripts written based on data jointly borne in the Study;
- The actual contribution by the Site and individual investigators shall be decisive when deciding who qualifies for an authorship in a particular manuscript.

If the results have not been published or an agreement of their imminent publishing reached within one year of the completion of the Study at each site, each site and/or Site-PI shall have the right to publish their results in accordance with generally accepted principles of scientific and ethical publishing and where applicable describing the divergent views due to which a joint publication by the Study Consortium was not possible.

Confidential Information, other party's Results or proprietary material shall not be disclosed when publishing unless published already earlier by the owning party of that Confidential Information or proprietary material. The parties are entitled to review the intended publications prior to publishing. The material which is intended to be published shall be delivered to the parties for approval in writing (including email). Restricting the publication shall be claimed no later than within thirty (30) days of receiving the material intended to be published. Restricting the publication may only be claimed on well-founded grounds, which may either be the protection of Confidential Information or protecting intellectual property rights included in the intended publication. Should this be the case, the parties shall negotiate amending the publication and avoid the situation, where the whole publication would be banned. If the parties have not expressed their well-founded and specified claim to restrict the publication within the said time limit, the publication shall be considered permitted.

15. ASSIGNMENT

The parties may not assign this agreement, any part thereof, or any right or obligation related thereto to any third party without a prior written consent of the other party. The parties are, however, entitled to assign their rights and obligations under the agreement to a third party to which the party's activities set forth in this agreement and its appendices is possibly being transferred to, when all rights and obligations under this agreement shall fully transfer to the transferee.

16. AMENDMENTS

All changes and amendments to this agreement shall be agreed upon in writing between the parties.

17. ENSURING CONDUCT OF THE STUDY

The Site shall be responsible for ensuring sufficient and appropriate resources for the conduct of the Study within the limits of the Study budget, and that no other than legal obligations or commitments of the Site of the Study cause unreasonable damage to or delay in conducting the Study as set forth in this agreement.

18. FORCE MAJEURE

Any event occurring after signing the agreement, which a party could not reasonably have taken into account at the time of the conclusion of the agreement and which prevents or delays the affected party from fulfilling its obligations under the agreement or makes the fulfillment thereof unreasonably difficult and which cannot be overcome without unreasonable loss of time or cost, shall constitute an event of force majeure. An event of force majeure shall include: strike, war, revolt, import or export prohibition, nature disaster, interruption of public traffic or distribution of energy, legal labor dispute, fire or any other reason having as severe and unusual effects beyond the control of the party.

If a party would wish to invoke existence of an event of force majeure as a cause for the non-compliance with any of its obligations under the agreement or delay or exemption from liability, it shall without delay inform the other party of the delay or termination of its contractual obligation in writing.

19. RETENTION AND DESTRUCTION OF STUDY RECORDS

The Site shall store the original Study records, results, and codes at minimum fifteen (15) years after the termination of the study. With respect to storage of records, the instructions set forth in Sections 4.9 and 5.5 of the ICH GCP are followed. The Coordinating Center shall notify the Site in good time in advance and in writing if it wants the Site to keep the records or codes after the abovementioned 15 years. The Coordinating Center shall notify the Site of the time after which the records related to the Study must no longer be stored, and reimburse the Site additional costs incurred by the storage exceeding fifteen (15) years. Alternatively, the Study records, results, and codes generated by the Site can be shipped to and stored at the Coordinating Center, if trusted so by the Site.

20. COMPLAINTS AND LIABILITIES

A party is obliged to notify the other party immediately in writing of all errors, omissions, and deficiencies detected in the conduct of the other party based on this agreement. Thereafter, the defaulting party has a duty to correct the reported error, omission, or deficiency.

A party shall be liable to compensate the other party the damages caused by its breach of contract. The parties shall not, however, be liable for any indirect or consequential damages, except for the damages caused deliberately or by gross negligence or which concern breach of confidentiality. The aggregate liability of a party shall be limited and shall not exceed 100% of the amount of the Study budget. The said limitation of liability set out herein shall not apply if the damage is caused by a wilful act or gross negligence.

21. TERM AND TERMINATION OF THE AGREEMENT

This agreement shall become effective upon signing by both parties. The agreement shall continue in effect until 31 Dec 2031, the presumed end of follow-up of patients, or until both parties have fulfilled their obligations set forth by this agreement.

Without prejudice to the term of the agreement, a party may terminate this agreement with immediate effect, if:

- The other party is in material default of any of its obligations under this agreement and the breach is of significant importance to the other party;
- The other party fails to comply with its obligations under this agreement and has not corrected its default, omission, or deficiency within four (4) weeks after the non-defaulting party has given the defaulting party written notice thereof; or
- The party has bankruptcy proceedings instigated against it or is placed into voluntary or involuntary liquidation or is declared insolvent or it is otherwise obvious that the party is unable to fulfill its obligations.

In the event a complaint as referred in Section 20 of this agreement has not led to correction of an error or deficiency, the Coordinating Center shall in addition have the right without separate obligation of compensation or refund to suspend the Study and terminate immediately in writing this agreement in the following circumstances:

- If the Site does not follow the protocol;
- If the Site fails to comply with the principles of the Good Clinical Practice guideline (GCP);
- If the Site-PI gives notice or is given notice by the unit conducting the study or otherwise ceases to work for the study as defined by this agreement, and the parties fail to reach mutual understanding on the new co-principal investigator; or
- If the Coordinating Center decides to terminate the Study for instance for scientific, ethical, or administrative reasons.

The terms and conditions and responsibilities relating to the rights of the Coordinating Center and the authorities, confidentiality of trade secrets, the Study register and personal data protection, data and records accrued as a result of the Study, intellectual property rights, publication of Results, archiving and destroying of the Study records and governing law and dispute resolution under Sections 10, 11, 12, 13, 14, 19, 22 and 23 of this agreement, shall survive termination or cancellation of this agreement.

22. GOVERNING LAW

This agreement shall be governed by the laws of Finland without regard to its conflict of laws rules.

23. DISPUTE RESOLUTION AND FORUM

All disputes arising out of or in connection with this agreement shall be resolved in the District Court of Helsinki if the parties fail to reach an amicable solution between themselves.

24. ENTIRE AGREEMENT

This agreement, including its Appendices, represents the entire understanding between the parties with respect to the conduct of the study as described in Section 2 and supersedes all prior oral or written agreements between the parties related thereto.

In case of a discrepancy between this agreement and its Appendices, this agreement shall prevail.

25. SIGNATURES

This agreement is executed in two (2) originals, one (1) for each party.

Time and Place:

____ / ____ 2021, Helsinki
Representative of the Coordinating Center: [redacted]
Title: CEO, HUS

Time and Place:

____ / ____ 2021, Helsinki
Representative of the Coordinating Center: [redacted]
Title: Research Director, HUS

Time and Place:

____ / ____ 2021, Almeria
Representative of the Site: [redacted]
Title: President

The undersigned is committed to work according to the Protocol and in all other ways promote the fulfillment of this agreement especially the responsibilities stated in section 6.

Time and Place:

____ / ____ 2021, Almeria

[redacted]
Site-PI

____ / ____ 2021, Almería

[redacted]
Managing Director Hospital de Torrecárdenas, Almería

____ / ____ 2021, Helsinki

[redacted]
Lead-PI

APPENDIX I: Study Protocol

APPENDIX II: Information Security Annex; HUS as a processor of personal data