HIT CF CLINICAL STUDY AGREEMENT

Clinical Trial to the Horizon2020 Project

Protocol: 'Stratifying Cystic Fibrosis Patients Based on Intestinal Organoid Response To Different CFTR-modulators' NL65123.041.18

Sponsor: UMC Utrecht

Institution: Fakultní nemocnice v Motole

Effective date of agreement: 01/NOV/2018 (dd-mmm-yyyy)

CLINICAL STUDY SITE AGREEMENT

The undersigned,

A. Universitair Medisch Centrum Utrecht, a legal entity existing under the laws of the Netherlands and governed by public law by virtue of the Dutch 'Wet op het hoger onderwijs en wetenschappelijk onderzoek' (Higher Education and Academic Research Act'), Division of Pediatrics, having its principle place of business at Heidelberglaan 100, 3584 CX, Utrecht, the Netherlands, hereinafter referred to as "UMC Utrecht", for this matter legally represented by

and

B. Fakultní nemocnice v Motole, state founded organization whose registered office is at Czech republic, Prague, V Úvalu 84/1, lawfully represented by
.
(hereinafter referred to as "**Study Site**")

in the presence of:

hereinafter referred to as "**Site Investigator**")

WHEREAS,

- the Parties each are partner to the Horizon 2020 project under the name 'Personalised Treatment For Cystic Fibrosis Patients With Ultra-rare CFTR Mutations and beyond' (hereinafter: 'HIT CF'), funded by the European Union;
- Together with other parties, Parties have entered into the HIT CF Consortium Agreement, describing the details of HIT CF;
- Part of HIT CF is a clinical study, which is briefly described in Annex 5 of the HIT CF Consortium Agreement;
- the Sponsor and in particular Kors van der Ent (hereinafter "**Investigator**"), researcher employed by Sponsor have designed the Clinical Study identified hereof;
- the Study Site has facilities and personnel with the requisite skills, experience, and knowledge required to support the performance of the Clinical Study by the Site Investigator;
- the Sponsor wishes to engage the Study Site and Site Investigator to perform part of the Clinical Study andSite Investigator and Study Site, having reviewed the Protocol and relevant Clinical Study information, is willing to participate in the Clinical Study;
- Part of the Study is the Material Transfer Agreement ('MTA' – attached as Annex 2)considering certain material (organoids), provided by STICHTING HUBRECHT ORGANOID TECHNOLOGY ('HUB'). HUB is a foundation that owns and controls certain patent rights and

know how to methods for obtaining, maintaining, expanding, differentiating, using and storing organoids *i.e.* the cell structures derived from primary epithelial (stem) cells from human or animal tissue from patients or healthy subjects ("**Organoids**");

In consideration of the undertakings and commitments set forth herein, the Parties agree to enter into this Clinical Study Agreement.

DEFINITIONS

The following words and phrases have the following meanings:

a. "**Agreement**" means this agreement comprising its clauses, schedules and any appendices attached to it, including the Protocol and including any amendments to the Agreement agreed between the Parties;
b. "**Clinical Study**" means the investigationas defined in the cadre on page 1 of this Agreement,(also) to be conducted at the Study Site in accordance with the Protocol as mentioned below;
c. "**Authorisation**" meansthe authorisation of a Clinical Study in accordance with the article 2 and (if applicable) 13i of the Dutch *Medical Research Involving Human Subjects Act*;
d. "**Clinical Study Subject**" means a person enrolled to participate in the Clinical Study;
e. "**Competent Authority**" means the authority appointed to evaluate the Clinical Study in accordance with 13i of the Dutch *Medical Research Involving Humans Subjects Act*, based on article 9 of the European Clinical Study Directive 2001/20/EC;
f. "**Confidential Information**" means any and all information, data and material of any nature belonging or entrusted to a Party and/or its affiliates, or which is a trade secret, which such Party (the "**Disclosing Party**") may disclose in any form to the other Parties (each a "**Receiving Party**") pursuant to this Agreement,the release of which is likely to prejudice the interests of the Disclosing Party;
g. "**CRF**" means the case report form in a format prepared by Sponsor and documenting the administration of the Study Drug to Clinical Study Subjects as well as all tests and observations related to the Clinical Study and "**eCRF**" means a CRF in electronic form;
h. "**Effective Date**" the date this Agreement comes into effect, being the date of the publishing in the Czech Contract Register;
i. "**Ethics Committee**" means the accredited medical research ethics committee competent to review the Clinical Study in accordance with applicable Law, and to which the Protocol has been submitted for approval;
j. **"ICF"** means the Informed Consent Form as approved by the Ethics Committee, in which the Subject consents to his participation in the Clinical Study;
k. "**Intellectual Property Rights**" means intellectual property rights including but not limited to patents, trade marks, trade names, service marks, domain names, copyrights, rights in and to databases (including rights to prevent the extraction or reutilisation of information from a database), design rights, topography rights and all rights or forms of protection of a similar nature or having equivalent or the similar effect to any of them which may subsist anywhere

in the world, whether or not any of them are registered and including applications for registration of any of them;

l. "**Law**" means any International, European Union and Dutch law and regulations, as well as generally accepted international conventions applicable to the performance of the Clinical Study. Such Law including but not limited to:
   - the Dutch Medical Research Involving Human Subjects Act (*Wet Medisch-wetenschappelijk Onderzoek met Mensen* or *WMO*),
   - the Dutch Personal Data protection Act (*Wet Bescherming Persoonsgegevens)*
   - the Dutch Medical Treatment Agreements Act (*Wet op de geneeskundige behandelingsovereenkomst* or *Wgbo*)
   - ICH Harmonised Tripartite Guideline for Good Clinical Practice (CPMP/ICH/135/95),
   - the Directives on "Review of Clinical Study Agreements" and on "External Review" issued by the Dutch Central Committee on Research involving Human Subjects (*Centrale Commissie Mensgebonden Onderzoek* or *CCMO*), and
   - the principles of the Dutch Code of Conduct regarding the adequate procurement, management and use of bodily human tissue published by the Federation of Dutch Medical Scientific Societies
   - and/or any successors of the above mentioned Laws.
   - Czech laws, particularly Act. No. 378/2007 Coll., on Pharmaceuticals, amended, Act. No. 372/2001 Coll., on health services, amended, Act. No. 101/2000 Coll., on personal data protection, amended, and notice 226/2008 Coll., on good clinical practice.

m. "**Party**" means the Sponsor or the Study Site and "Parties" shall mean the two of them jointly;

n. "**Protocol**" means the document as defined in the cadre on page 1 of this Agreement, detailing all aspects of the Clinical Study, and for which Authorisation has been obtained, a copy of which is at Annex 1 to this Agreement. The Protocol includes all amendments thereto for which Authorisation has been obtained;

o. "**Research Staff**" means the persons who will undertake the conduct of the Clinical Study at the Study Site on behalf of the Site Investigator and under the supervision of the Site Investigator;

p. "**Site Investigator**" means the person who will take primary responsibility for the conduct of the Clinical Study at the Study Site or any other person as may be agreed from time to time between the Parties as a replacement;

q. **"Site Parties"** mean Study Site and Site Investigator;

r. "**Study Drug**"means the study drug provided by Sponsor to Study Site in accordance with the Protocol;

s. "**Study Monitor**" means one or more persons appointed by the Sponsor to 1) monitor compliance of the Clinical Study with GCP and the Protocol and to conduct source data verification or 2) conduct a systematic and independent examination of trial-related activities and documents to determine whether the evaluated trial-related activities were conducted, and the data were recorded, analyzed, and accurately reported according to the protocol, sponsor's standard operating procedures (SOPs), GCP and the applicable regulatory requirement(s)";

1. OBLIGATIONS

1.1. The Site Parties agree to perform the Clinical Study in accordance with the terms and conditions of this Agreement.

1.2. The Site Parties represent and warrant that they each have the authority to enter into this Agreement. The Site Investigator will ensure the availability of and/or access to any resources necessary to perform the Clinical Study at the Study Site, including departments, facilities and Research Staff and support personnel, and represents that he/she holds the necessary registration and has the necessary qualifications, expertise and time to perform the Clinical Study.

1.3. The Site Investigator shall notify the Sponsor if he/she ceases to be associated with the Study Site where the Clinical Study will be conducted or if he/she is otherwise unavailable to continue as Site Investigator, and Study Site shall use all reasonable endeavours to find a qualified successor acceptable to the Sponsor. Replacement of the Site Investigator is subject to authorisation by the Ethics Committee. If subject to the foregoing no mutually acceptable replacement can be found, within reasonable time as not to hinder the safe continuation of the Clinical Study at the Study Site, and provided that the Sponsor will not unreasonably withhold its approval of the proposed replacement of Site Investigator, each Party may terminate this Agreement pursuant to clause 10.2.g below.

2. CLINICAL STUDY GOVERNANCE AND COMPLIANCE

2.1. The Sponsor shall be responsible for obtaining and maintaining Authorisation for the Clinical Study and (substantial) amendments to the Protocol.

2.2. In the event of any substantial amendments being made to the Protocol, the amendments shall be signed by the Site Investigator and shall be implemented after Authorisation and a favourable opinion of the Ethics Committee.The Site Investigator shall not consent to any change in the Protocol requested by the Ethics Committee or Competent Authority without the prior written consent of the Sponsor.

2.3. The Clinical Study shall be performed at the Study Site. The Site Investigator shall be responsible for obtaining permissionfrom the representatives of the Study Site to perform the Clinical Study at the Study Site, which shall includethe engagement of the Research Staff and, to the extent applicable, the pharmacist of the Study Site andclinical chemists.

2.4. The Sponsor shall be responsible for submitting the Clinical Study for listing on a free, publicly accessible clinical studyregistry.

2.5. The Parties shall conduct the Clinical Study in accordance with the Protocol,this Agreement and applicable Law.

2.6. The Site Investigator shall submit CRF/eCRFs to the Sponsor as outlined in the Protocol.

3. LIABILITIES, INDEMNIFICATION AND INSURANCE

3.1 Subject to the limitations set out hereinafter, Sponsor, being the insurance holder as set out in clause 3.7 below, shall indemnify and hold harmless Study Site, its employees, the Site Investigator and the Research Staff (the "Indemnitees") against all claims, demands, actions or proceedings (to include any settlements or ex gratia payments made with the consent of the Parties hereto and reasonable legal and expert costs and expenses) made or brought (whether successfully or otherwise): (i) by or on behalf of any Subject for personal injury or death arising out of the administration or use of the Study Drug during or as a result of the Clinical Study, orof any clinical intervention or procedure provided for or required by the Protocol, to which the Subject would not have been exposed but for its participation in the Clinical Study; (ii) by Study Site, the Site Investigator or by or on behalf of aSubject for compensation of reasonable and necessary medical costs and expenses incurred by theSubject who has suffered personal injury as described in 3.1.(i) above.

3.2 Sponsor's indemnification and defence of the Indemnitees shall not apply to any claim or proceeding pursuant to clause 3.1, and Sponsor shall not be liable:

(a) to the extent that said personal injury (including death) is caused by any of the Indemnitees' failure to comply with this Agreement or the Protocol; or

(b) to the extent that said personal injury (including death) is caused by gross negligence recklessness or willful conduct or misconduct (in Dutch: bewuste roekeloosheid of opzettelijk handelen of nalaten) of any of the Indemnitees, unless the clinical trial insurance of Sponsor is providing coverage for the claim.

3.3 Parties shall keep each other reasonably informed of developments in relation to any such or proceeding. Parties will consult with each other on the nature of any defence to be advanced.

3.4 Parties will each give to the other such help as may reasonably be required for the efficient conduct and prompt handling of any claim or proceeding made or brought by or on behalf of Clinical Study Subjects (or their dependants).

3.5 Except in the event of intentional behaviour or gross negligence of a Party, in no event will a Party's liability towards the other Party include any indirect damages (indirect damages meaning: loss of profit, loss of revenue and loss of business opportunities).

3.6

3.7 If and to the extent required, Sponsor shall arrange insurance cover in respect of its potential liability for damages to Clinical Study Subjects resulting from the Clinical Study, unless this requirement has been waived by the Ethics Committee.

3.8 Both Study Site and Sponsor shall take out and maintain an insurance cover in respect of their potential liability in connection with the conduct of the Clinical Study.

4. SUBJECT RECRUITMENT AND ENROLLMENT

4.1. The Site Investigator shall use reasonable endeavours to recruit (a maximum of) Clinical Study Subjects to the Clinical Study within the timelines specified in the Protocol; however the Clinical Study is estimated to begin in with the end of Study estimated to be Site Investigator shall make sure that the Clinical Study Subjects (and/or their legal representatives, if applicable) will, in accordance with applicable legislation and the guidelines of ICH GCP if applicable, be duly informed prior to their participation in the Clinical Study, in a language the Subjects (and/or their legal representatives, if applicable) can fully understand on all aspects of the Clinical Study which are deemed relevant in their decision to participate, and give informed consent.

4.2. If circumstances or events have occurred or will occur that will substantially delay or are likely to substantially delay the progress of recruitment or enrolment of the Clinical Study Subjects, the Site Investigator shall immediately inform the Sponsor in writing. In each such event Parties shall discuss the consequences of the delay and each Party shall undertake reasonable endeavours to agree on measures to overcome the delay.

4.3. In the event that the Clinical Study is part of a multi-centre clinical Study, the Site Investigator acknowledges and agrees that recruitment may be competitive and that Sponsor may stop further recruitment of Clinical Study Subjects at the Study Site when the recruitment target for all investigational sites for this Clinical Study has been met, even if the Study Site has not yet recruited the amount of Clinical Study Subjects pursuant to clause 4.1.

5. QUALITY ASSURANCE AND CONTROL

5.1. The Study Site shall permit the Study Monitor and any official with a legal right to inspect and access all relevant documentation and source data for monitoring or auditing of the progress of the Clinical Study, the proper collection and recording of Clinical Study data, the welfare of the Subjects, and altogether the good quality of the Clinical Study and compliance with applicable Law and Sponsor's Standard Operating Procedures.The Study Monitor's access will be arranged at mutually convenient times and on reasonable notice with no additional costs for the Study Monitor or Sponsor, after Sponsor has provided Study Site the contact details of the Study Monitorand the inspection shall not disrupt the routine operation of the Study Site.The Study Monitor will comply with all internal policies and regulations of the Study Site during such inspection.For the avoidance of any doubt, the Sponsor shall be responsible for the confidential handling of all personal data of Subjects and other patients which the StudyMonitor or Sponsor comes across with during such inspection and will let the Study Monitor sign a confidentiality declaration prior to such inspection.Prior to any monitoring or auditing by the Study Monitor, Sponsor shall provide a completed monitoring instruction letter as attached in Annex 4 covering each individual Study Monitor.

5.2. The Site Investigator or the Study Site shall promptly inform the Sponsor of any intended or actual inspection, written enquiry and/or visit to the Study Site by any

regulatory authority in connection with the Clinical Study and forward to the Sponsor copies of any correspondence from any such regulatory authority relating to the Clinical Study. The Site Parties shall allow Sponsor's representatives to be present during any such visit.

5.3. The Site Investigator shall take appropriate measures and/or corrective actionswithout delay as the Sponsor may reasonably require in order to solve all problems found and reported by the Study Monitors or officers from regulatory authorities or during an inspection under clause 6.3.

6. CONFIDENTIALITY

Medical Confidentiality

6.1. It is the responsibility of each Party to effect and maintain all registrations for the processing of Personal Data(meaning personal data as referred to in laws and regulations applicable in the Netherlands) as required by the Dutch and Czech privacy laws and legislations, which includes the General Data Protection Regulation. Each Party shall be responsible for its own processing of personal data in accordance with all law and regulations and with the informed consents obtained from Subjects.

6.2. The Parties and the Site Investigator agree to adhere to the principles of medical confidentiality (in accordance with the laws and regulations applicable in The Netherlands in relation to Clinical Study Subjects involved in the Clinical Study). Personal Data of Clinical Study Subjects shall not be disclosed to Sponsor by Study Site or Site Investigator unless this is required to satisfy the requirements of the Protocol or for the purpose of monitoring or adverse event reporting, or in relation to a claim or proceeding brought by the Clinical Study Subject in connection with the Clinical Study. Such disclosure of Personal Data of Clinical Study Subjects can only take place with the expressed written informed consent of the Clinical Study Subject.Parties shall process personal data in compliance with security standards essentially equivalent to those required by the laws and regulations applicable in The Netherlands.

6.3. Sponsor shall refrain from tracing and/or identifying any Clinical Study Subject. In the event any Clinical Study Subject, for whatever reason, becomes identifiable to Sponsor, Sponsor agrees to preserve, at all times, the confidentiality of information pertaining to such Clinical Study Subjects. Sponsor shall adopt appropriate technical and organizational measures to prevent any unauthorized or accidental use, access or processing of clinical data and/or Organoids (Security Breach). Security Breaches shall be reported to the Site Investigator promptly.

Confidential Information

6.4. The receiving Party shall ensure that only those of its officers and employees concerned with the carrying out of this Agreement have access to the Confidential Information of the disclosing Party. The receiving Party shall take all practicable steps to ensure that such persons abide by the same obligations of confidentiality as apply to the receiving Party under this Agreement. The receiving Party undertakes to treat as strictly confidential and not to disclose to any third party any Confidential Information of the

disclosing Party, except where disclosure is required by a regulatory authority or by law, in which case the receiving Party shall inform the disclosing Party of such requirement and the information to be disclosed. Notification will be within a reasonable time prior to being required to make the disclosure or if such time is not available, immediately upon becoming known of the requirement to disclose, Confidential Information. The receiving Party undertakes not to make use of any Confidential Information of the disclosing Party, other than in accordance with this Agreement, without the prior written consent of the disclosing Party.

6.5. The obligations of confidentiality and non-use set out in clause 6.4 shall not apply to information which the receiving Party can show by competent evidence:

a. is or becomes part of the public domain by any other means than a wrongful act or breach of this Agreement by the receiving Party;
b. was or becomes in the receiving Parties' lawful possession prior to the disclosure without restriction on disclosure;
c. has been independently developed by the receiving Party without the use of Confidential Information of the disclosing Party;
d. has been obtained by the receiving Party from a third party without breach of a confidentiality obligation; or
e. is published in accordance with clause 9 hereof.

Site Investigator and Research Staff's Personal Information

6.6 To the extent this clause 6.6 is applicable, Sponsor shall provide the Institution specific forms on which the Site Investigator and Research Staff shall be requested to consent to use of their personal data for the following purposes. Site Investigator and Research Staff understand and agree that their personal information including name, contact details, financial information relating to, among other matters, compensation and reimbursement payments for study conduct, and other personal data of the Site Investigator and Research Staff in connection with Site Investigator's and Research Staff's conduct of the Clinical Study will be processed both by computer and manually, by Sponsor and its Affiliates and Agents in order to comply with Sponsor's and its Affiliates' obligations imposed by law, guidance or regulatory authorities and for considering from time to time potential investigators for future studies or organizing safety reporting.Site Investigator and Research Staff further understand and agree that their personal data may, if necessary for these purposes, be made available to regulatory authorities and ethics committees. Site Investigator and Research Staff understand and agree that the Sponsor may be required to disclose their personal data to the external funder of the Clinical Study (if applicable) andthat such may involve use and disclosure in countries other than that where the Site Investigator and Research Staff are located.Such countries may include but not be limited to: the United States, Japan, Canada, Australia, New Zealand, Switzerland, or countries in Latin America or Asia.Site Investigator and Research Staff further understand that not all countries to which personal information may be transferred offer an equivalent level of protection of privacy of personal information.

The Sponsor can disclose personal data to the external funder as mentioned aboveonly after external funder's prior written agreementupon conditions at least as strict as those contained in this Agreement and in accordance with the laws and regulations applicable in the Netherlands and the Czech republicand without the right to any further sublicense or transfer.

Site Investigator and Research Staff are entitled to review their personal data held by Sponsor upon request and to have such data corrected if necessary.

7. INTELLECTUAL PROPERTY

Intellectual Property Rights are part of the HIT CF Consortium Agreement (annex 3/ Section 8.0 and 8.1 of the HIT CF Consortium Agreement).

8. PUBLICITY

The Sponsor will not use the logo or name of the Study Site, Site Investigator, nor of any member of the Research Staff, for promotional purposes, in any publicity, advertising or news release without the prior written approval of the Study Site or Site Investigator, such approval not to be unreasonably withheld. The Study Site and Site Investigator will not, and will ensure that the Research Staff will not, use the name or logo of the Sponsor or of any of its employees for promotional purposes, in any publicity, advertising or news release without the prior written approval of the Sponsor, such approval not to be unreasonably withheld.

9. PUBLICATION AND AUTHORSHIP

Publication and authorship are part of the HIT CF Consortium Agreement (annex 3/ Section 8.3 of the HIT CF Consortium Agreement).

10. TERM AND TERMINATION

10.1. This Agreement commences on the Effective Date and shall continue in force until the earlier of:

a. completion of the Clinical Study, close-out of the Study Site and completion of the obligations of the Parties under this Agreement; or

b. early termination in accordance with clauses 10.2 or 10.3 of this Agreement;

10.2 Each Party may terminate this Agreement upon written notice to the other Parties with immediate effect in the following events:

a. if the approval by the Ethics Committee is irrevocably revoked;

b. if it can be reasonably assumed that the Clinical Study must be terminated in the interests of the health of the Subjects;

c. if it becomes apparent, following confirmation of the Ethics Committee or the Independent Committee (if applicable), that continuation of the Clinical Study cannot serve a scientific purpose, and this is notified to the Ethics Committee;

d. if the Sponsor and/or the Institution become or are declared insolvent or a petition in bankruptcy has been filed against it or if one of them is dissolved;

e. if circumstances beyond a Party's control occur that render continuation of the Clinical Study unreasonable;

f. if one of the Parties fails to comply with the obligations arising from the Agreement and, if capable of remedy, is not remedied within 30 days after receipt of notice from the other Party specifying the non-compliance and requiring its remedy, unless the severity of the failure to comply does not reasonably justify the premature termination of the Clinical Study; or

g. if the Site Investigator is no longer able (for whatever reason) to act as Investigator and no mutually acceptable replacement has been found in accordance with clause 1.3.

10.3 Sponsor may terminate this Agreement upon written notification to the Site Investigator and the Study Site for lack of recruitment at the Study Site. The foregoing provided however, that this clause 10.3 shall not apply and Sponsor shall have no right to terminate this Agreement if any Subject has undergone treatments or conduct has been imposed on the Subject as per the Protocol, at the Study Site.

10.4 At close-out of the Study Site following termination or expiration of this Agreement the Site Investigator and the Study Site shall immediately return to the Sponsor all Confidential Information, equipment and/or unused materials provided by Sponsor in accordance with Sponsor's instructions, except for one copy of the Confidential Information for archival and evidentiary purposes.

10.5 Sponsor undertakes to deliver to the Study Site a modified version of the Agreement, in the appropriate electronic format for submitting for publication in the public registry of agreements pursuant to the Act no. 340/2015 Coll., on Special Conditions for the Effectiveness of Certain Contracts, the Disclosure of These Contracts and the Register of Contracts; , as amended (hereinafter the "Contracts Register Act"); not later than by the date of signing a full version of the Agreement. The Study Site undertakes to submit such modified version of the Agreement for publication within 30 (thirty) days from the Agreement signature by the Provider.

In the register of contracts, following confidential information according to this contract including: all personal data of individuals all contact details, in addition anybusiness secrets within the meaning of Section 504 of Act No. 89/2012 Coll., The Civil Code, which, by agreement of the contracting parties includes: study protocol, Study design, detailed breakdown budget, duration of the study, number of subjects and related subject approved expenses.

The Study Site will notify the following about the

11. FINANCIAL PROVISIONS / STUDY DRUG / MATERIAL / EQUIPMENT

11.1. The Sponsor will not provide Financial reimbursement in support of the Clinical Study.

11.2. Financial reimbursement for transfer of Material to HUB is determined in the MTA with HUB (annex 2).The total amount of the financial reimbursement is estimated to be the

amount of 4.000,00 euros (750,00 euros for start-up costs and 3.250,00 euros for patient insurance).

12. FORCE MAJEURE

13.1 No Party shall be liable to the other Parties or shall be in default of its obligations hereunder if such default is the result of war, hostilities, terrorist activity, revolution, civil commotion, strike, and epidemic or because of any other cause beyond the reasonable control of the Party affected. The Party affected by such circumstances shall promptly notify the other Parties in writing when such circumstances cause a delay or failure in performance and where they cease to do so.

13. MISCELLANEOUS

13.1. No Party may assign its rights under this Agreement or any part thereof without the prior written consent of the other Parties, such consent not to be unreasonably withheld or delayed, and no Party may sub-contract the performance of all or any of its obligations under this Agreement without the prior written consent of the other Parties, such consent not to be unreasonably withheld or delayed. Any Party who so sub-contracts shall be responsible for the acts and omissions of its sub-contractors as though they were its own.

13.2. Nothing in this agreement shall be construed as creating a joint venture, partnership or contract of employment between the Parties.

13.3. Should there be a conflict between the terms and conditions of the Protocol and the Agreement concerning clinical, ethical or medical matters, the Protocol shall prevail; in all other matters, the Agreement shall prevail.

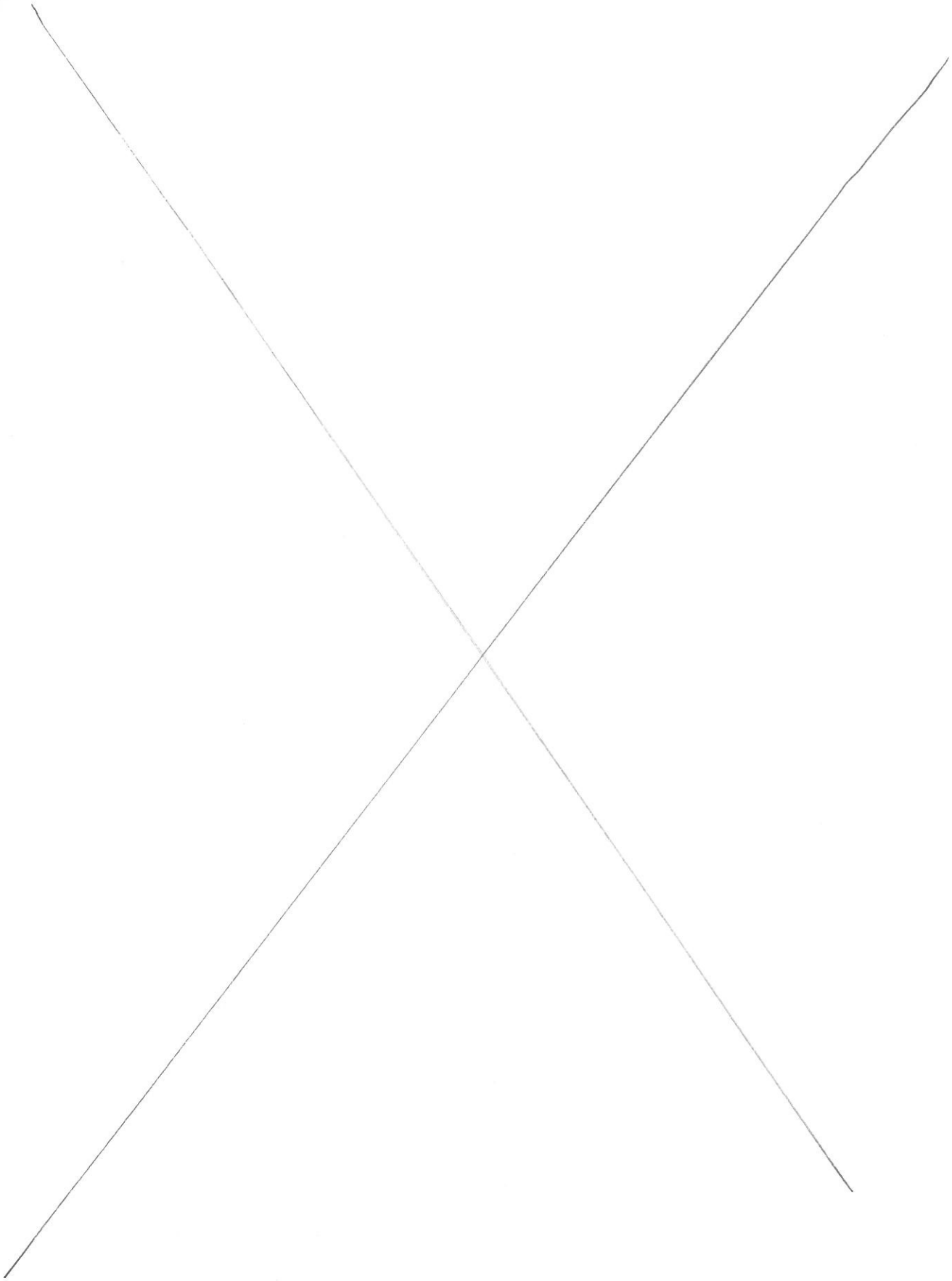
13.4. The clauses 3(Liabilities, Indemnification and Insurance); 5.1 and 6.3(Quality Assurance and Control); 6(Confidentiality).; 7(Intellectual Property); 8(Publicity); 9(Publication and Authorship); 10.4 (Term and Termination); 11(Financial Provisions); this clause 13.4 (Surviving Clauses), 13.5 (Governing Law), 14(Organoids) or other clauses contemplating performance after termination, shall survive termination or expiry of this Agreement. The provisions of clause 6.4 and 6.5 (Confidential Information) shall remain in force for a period of five (5) years.

13.5. This Agreement shall be governed by, and construed in all respects in accordance with the laws of The Czech republic without regard to its conflicts of laws rules. Any claims, controversies or disputes arising out of or in connection with this Agreement which cannot be settled amicably between the Parties, shall be subject to the exclusive jurisdiction of the competent court in The Czech republic.

13.6. This Agreement is executed in 2 counterparts, one for each of the Party.

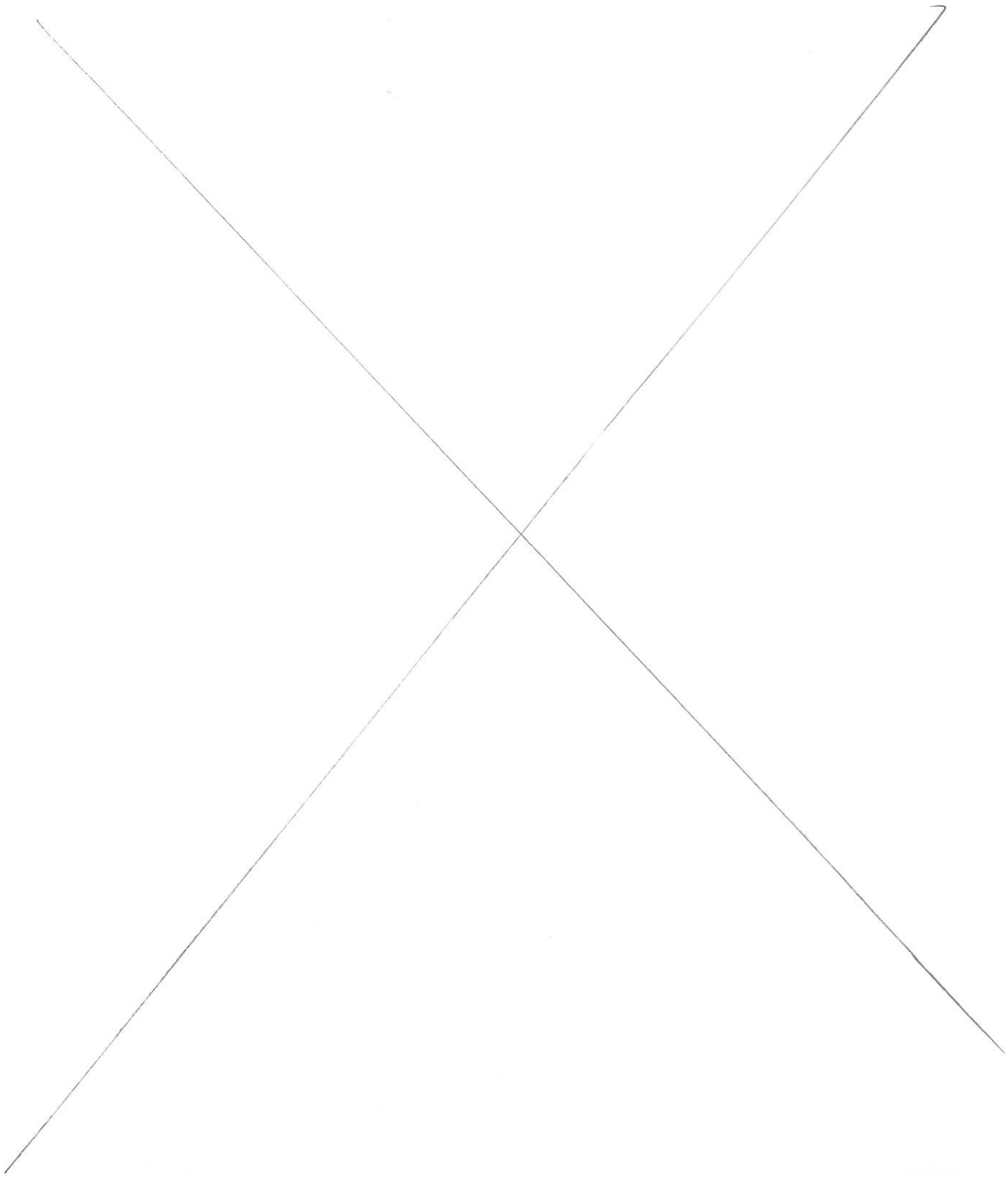
14. ORGANOIDS

14.1 As part of the Protocol, certain patient material derived from Clinical Study Subjects may be transferred to HUB, as arranged for in the ICF and the MTA.The MTA forms an integral part of this Agreement.



Annexes

Annex 1: Protocol
Annex 2: MTA with HUB
Annex 3: Relevant provisions of the HIT CF Consortium Agreement
Annex 4: Monitoring instruction letter



Signed on behalf of the **Sponsor**

Signatur
Name
Title:
Date: 8 - 11 - 2018

Signature:
Name:
Title:
Date: 12 NOV 2018

Signed on behalf of the **Study Site**

Signature:
Name:
Title: director
Date: 26. 11 2018

The undersigned Site Investigatorhereby declares that he/she has read the above Agreement between the Parties and that he/she agrees with the provisions of the Agreement relative to his/her role, responsibilities and duties concerning the Clinical Study;

Signed by the **Site Investigator:**

Signature:
Name:
Title: Site investigator
Date: 22.11.2018

ANNEX 1

PROTOCOL

(by reference only)

ANNEX 2

MTA with HUB

ANNEX 3

HIT CF Consortium Agreement

INTELLECTUAL PROPERTY

8.0 Intellectual Property Rights

All Intellectual Property Rights and Know How owned by or licensed to any of the Parties prior to and after the date of this Agreement other than any Intellectual Property Rights and Know How arising from the Clinical Study are and shall not be affected by this Agreement.

Inventorship of Intellectual Property Rights shall be determined in accordance with applicable Belgian law.

The Pharmaceutical Company that supplied the relevant Study Drug shall own the Intellectual Property Rights and Know How arising from and directly related to such Study Drug (including but not limited to its formulation and use alone or in combination with other drugs). Stichting Hubrecht Organoid Technology shall own the Intellectual Property Rights and Know How arising from and directly related to the HUB Organoid Technology and the HUB Organoids. This excludes (1) any clinical procedure and improvements thereto that are clinical procedures of the Study Site and (2) copyrights on work published by a Party which copyrights shall vest in the Study Site in accordance with applicable copyright laws or as mutually agreed between the Parties, or shall vest in the publisher of such work upon the transfer of copyrights by the author(s).

8.1 Results

Any Results unrelated to the Study Drug shall be owned by the party or Parties generating such Results. Results that relate to the Study Drug shall be jointly owned by the Parties that generated the Results and the Party that supplied the Study Drug to which such Results are related. Results that relate to the HUB Organoid Technology and/or the HUB Organoids shall be jointly owned by the Party that generated the Results and Stichting Hubrecht Organoid Technology.

For avoidance of doubt, the abovementioned paragraph only relates to the parties to the HIT CF Consortium Agreement and not to the Study Site. The results arising from this Clinical Study under this Agreement shall be solely owned by the Sponsor.

The academic Parties are allowed to use Results that relate to the Study Drug and Results that relate to the HUB Organoid Technology and/or the HUB Organoids for their internal hospital and/or non-commercial research and/or educational activities and for publication purposes, to the extent such use does not result in the disclosure or misuse of Confidential Information or the infringement of any Intellectual Property Rights thereto of the Pharmaceutical Companies or the Stichting Hubrecht

Organoid Technology. The Pharmaceutical Companies and Stichting Hubrecht Organoid Technology shall be able to use their respective Results for all purposes.

PUBLICATION AND AUTHORSHIP

8.3 Dissemination

8.3.1 Dissemination of own Results

8.3.1.1 During the Project and for a period of 4 years after the end of the Project, the dissemination of each Party's own Results shall be governed by the procedure of Article 29.1 of the Grant Agreement subject to the following provisions.

Prior notice of any planned publication shall be given to the other Parties at least 45 calendar days before the publication. Any objection to the planned publication shall be made in writing to the Coordinator and to the Party or Parties proposing the dissemination within 30 calendar days after receipt of the notice. The objection has to include a precise request for necessary modifications. If no objection is made within the time limit stated above, the publication is permitted. This provision shall not be taken to imply editorial control in order to intentionally prevent the dissemination of Results.

8.3.1.2 An objection is justified if

(a) the protection of the objecting Party's Results, Intellectual Property Rights or Background would be adversely affected

(b) the objecting Party's legitimate interests in relation to the Results, intellectual Property Rights or Background would be significantly harmed.

The objection has to include a precise request for necessary modifications.

If an objection has been raised the involved Parties shall discuss how to overcome the justified grounds for the objection on a timely basis (for example by amendment to the planned publication and/or by protecting information before publication) and the objecting Party shall not unreasonably continue the opposition if appropriate measures are taken following the discussion.

The objecting Party can request a publication delay of not more than 90 calendar days from the time it raises such an objection. After 90 calendar days the publication is permitted, provided that Confidential Information of the objecting Party has been removed from the Publication as indicated by the objecting Party (to the extent the scientific integrity of the Publication is as such not jeopardized, it being understood that any objections based on IP concerns of the objecting Party shall always be taken into account and such removal of Confidential Information shall always be implemented).

8.3.2 Dissemination of another Party's unpublished Results or Background

A Party shall not include in any dissemination activity entailing another Party's Results or Background without obtaining the owning Party's prior written approval, unless they are already published.

8.3.3 Cooperation obligations
The Parties undertake to cooperate to allow the timely submission, examination, publication and defence of any dissertation or thesis for a degree, which includes their Results or Background subject to the confidentiality and publication provisions agreed in this Consortium Agreement.

8.3.4 Use of names, logos or trademarks
Subject to article 8.3.5 hereafter, nothing in this Consortium Agreement shall be construed as conferring rights to use in advertising, publicity or otherwise the name of the Parties or any of their logos or trademarks without their prior written approval. Regarding to the new HIT-CF website and other project related communication, all parties agree with the use of their logo and contact details to inform the general public on the composition of the consortium.

8.3.5 Acknowledgement of Scientific Contribution
Any Dissemination (communication or publication) related to the Results generated by a Party shall mention the name and recognize the contribution of such Party and its scientists involved in the Project in accordance with customary scientific practice.

8.4 Section 8 will apply to the extent permitted by applicable law.

ANNEX 4

Monitoring instruction letter

Risk classification

The estimated risk of this study has been assessed as "negligible" by the sponsor.

Monitoring

Monitoring at UMC Utrecht will be performed by a central appointed person. Foreign sites will be visited once during the study for monitoring purposes by a member of the study team. Sponsor will make sure monitoring in participating sites is executed.

Frequency of monitoring

For each foreign participating site 1 monitoring visit will be performed, scheduled as close as possible after the date the first 3 subjects are included.

Further on, an "initiation visit" and "close out visit" will be performed. For foreign sites this will be done via teleconference call.

Source Data Verification

- 10% check on presence and accuracy of completed Informed Consent (ICF) forms.
- 100% check on in- and exclusion criteria of the first 3 subjects. Subsequently 10% of the remaining subject will be checked on in- and exclusion criteria. In the event that wrongly-included subjects have been included in the study, all files can be checked.
- 100% verification of reported SAEs en SUSARs.
- 10% of the subjects will be checked for missing SAE's.

General control

- Per monitoring visit the inclusionrate and drop out percentage will be reported.
- The presence and completeness of the Investigator Site File shall be checked and at sponsor site also the Study Master File will be assessed.

- The presence of Standard Operating Procedure (SOP)s will be verified as well as compliance and training on SOPs.
- A check on appliances and facilities will be performed to see if quality standards are met.

Monitoring Report

Monitor will write an report to the Sponsor of every Monitoring Visit that took place. This report will be filed at the Trial Master File. The local Investigator will also receive a written report containing a summary of the Monitoring Visit and of any findings that may have been done.

The Monitoring Report contains:

- A summary of items assessed by the Monitor.
- A general description of quality.
- A list of important findings/facts, deviations or missing data.
- An overview of required actions and recommendations to assure fulfilment of the protocol.
- "Overall" conclusion.

Sponsor also receives the Initiation Visit Report as well as the Close Out report.

MATERIAL TRANSFER AGREEMENT

(HUB as recipient)

THIS MATERIAL TRANSFER AGREEMENT (the "**MTA**") is signed on the date last set below (the "**Effective Date**") by and between:

1. STICHTING HUBRECHT ORGANOID TECHNOLOGY, a foundation duly organised and existing under the laws of the Netherlands, having its registered offices at Yalelaan62, (3584 CM) Utrecht, the Netherlands, registered in the Chamber of Commerce under number 58706542, for this matter legally represented b , (hereinafter referred to as "**HUB**");

   and

2. Fakultnínemocnice v Motole, a state budgetary institution duly organised and existing under the laws of the Czech republic, having its registered address at Czech republic, Prague, V Úvalu 84, 156 00, ID 000 64 203, for this matter legally represented by its (hereinafter referred to as "**Provider**");

Each of HUB and Provider individually referred to as a "**Party**" and jointly referred to as the "**Parties**".

WHEREAS:

A. HUB is a foundation that owns and controls certain patent rights and know how to methods for obtaining, maintaining, expanding, differentiating, using and storing organoids *i.e.* the cell structures derived from primary epithelial (stem) cells from human or animal tissue from patients or healthy subjects ("**Organoids**");

B. HUB is party to the Horizon 2020 project under the name 'Personalised Treatment For Cystic Fibrosis Patients With Ultra-rare CFTR Mutations (and beyond)', under which project the collaborating parties aim to set up an European biobank of CF organoids (the "**Project**");

C. Provider is a university hospital involved in providing health careand has access to Material (as defined below);

D. HUB desires to receive certain Material, to use such Material for academic and commercial research purposes in accordance with the informed consent form as attached to this MTA as Exhibit A ("**ICF**") and Provider is willing to provide such Material to HUB, subject to the terms and conditions of this MTA and all applicable laws and regulations.

THE PARTIES AGREE AS FOLLOWS:

1. MATERIAL

1.1. **Material** shall mean the material further specified in the Material Transfer Form as attached to this MTA in Exhibit Bfor each transfer, as well as any modified and non-modified derivatives, progeny and descendants obtained directly or indirectly from the original material (including, but not limited to, organoids), as well as any composition containing

the same. Material shall further be deemed to include all information and documentation related to the Material as provided by Provider.

1.2. Provider shall collect the Material in accordance with the ICF and transfer the Material to HUB subject to the terms and conditions of this MTA.

1.3. HUB shall solely use the Material for academic and commercial research purposes within the scope of the ICF and in compliance with all applicable laws and regulations. HUB shall not use the Material in or on humans.

1.4. The costs for the transfer of the Material to HUB, including such costs as custom's clearance, transportation and insuranceshall be paidin accordance with the Project and the allocated budget. . HUB and Provider shall in mutual consultation decide on the details of the transport. In deviation of art. 11.2 of the HIT-CF Clinical Study Agreement as signed between Provider and Universitair Medisch Centrum Utrecht, the cost for the transfer of the Material to HUB shall not be reimbursed by HUB to Provider but covered by the Project budget.

2. PERSONAL DATA

2.1. Provider hereby represents and warrants to HUB that the Material that is transferred to HUB under this MTA is:

i. collected in accordance with all applicable laws and regulationsand that the ICF as attached in Exhibit A is signed by the donor or its legally authorized representative; and

ii. is coded by Provider in such a way that it cannot be used by HUB to reasonably identify the person from whom the Material is derived, regardless of the medium in which such information is displayed.

2.2. To the extent that the Material constitutes human material, Provider shall maintain, document and retain records of informed consent from each donor or the donor's legally authorized representative in accordance with applicable laws and regulations.

2.3. Parties recognize that any Material disclosed under this MTA may constitute personal data as defined in Directive 95/46/EC or the General Data Protection Regulation 2016/679 as amended or superseded from time to time. HUB shall comply with all applicable laws, standards and regulations in using the Material. For the avoidance of doubt, HUB shall not perform any act which would lead to the identification of the donors concerned, including by linking different sets of data, comparing and processing data.

2.4. HUB acknowledges and agrees that the donor of the Materialor its authorized representativeshall at all times have the right to request HUB to destroy its Material. In such event, Provider shall promptly inform HUB thereof in writing. HUB shall procure that the Material is destroyed, provided however that, in accordance with the ICF, Material that is part of a (clinical) study cannot be retracted. Other than for such organoids, HUB shall confirm the destruction of the Material in writing to Provider within 2 (two) weeks of receipt of the written notice by Provider.

2.5. In the event the Material is not of sufficient quantity or quality to generate an organoid, HUB shall inform Provider thereof in writing and shall destroy any remaining Material upon its request.

3. CONFIDENTIALITY AND INTELLECTUAL PROPERTY

3.1. Nothing in this MTA will prevent the receiving Party from disclosing confidential information where it is required to do so to comply with a court order, applicable laws or governmental regulations provided that the receiving Party, where possible, notifies the disclosing Party of such requirement prior to any such disclosure so that the disclosing Party may seek a protective order or similar protection for the confidential information.

3.2. The obligations of confidentiality set forth herein shall expire five (5) years after expiration or early termination of this MTA.

3.3. HUB shall own all right, title and interest in and to the data, results, know how or other intellectual property generated, conceived or reduced to practice by HUB using the Material in accordance with this MTA.

4. TERM AND TERMINATION

4.1. This MTA shall enter into force on the Effective Date and shall remain in force until the Projecthas been completed or otherwise terminated, or until this MTA is terminated in accordance with this Article 4, whichever is the earlier.

4.2. Either Party may terminate this MTA upon written notice to the other Party with immediate effect in case of any material breach of or failure to comply with any of the terms or conditions of this MTA by the other Party, which breach or failure, if capable of remedy, is not remedied within thirty (30) days after notice from the aggrieved Party demanding such remedy.

4.3. In case of termination of this MTA by Provider in accordance with Section 4.2, HUB shall, upon the written request of Provider, return or destroy all Material received from Provider. Upon expiration or termination of this MTA, HUB shall remain entitled to use the Material subject to Section 2.4.

4.4. Those provisions that by their nature are intended to survive termination or expiration of this Agreement shall so survive, including Article 2 (Personal Data), Article 3 (Confidentiality and Intellectual Property), Article 5 (Liability), Article 6 (Miscellaneous), whereby the confidentiality obligations of Article 3 shall survive for a five (5) year period.

5. LIABILITY

5.1. Except as otherwise set out in this MTA, Parties agree that the Material is experimental in nature and is provided "as is" without any warranties, express or implied, including any warranty of merchantability or fitness for a particular purpose, or that the use of the Material will not infringe any patent, copyright, trademark, or other proprietary rights.

5.2. Each Party (for the purpose of this Article 5, the "**Indemnifying Party**") shall indemnify and hold harmless the other Party and its officers, directors and employees for any damages or expenses(including reasonable attorneys' fees), resulting from any (third party) claim, suit or proceeding brought against that Party rising out of in connection with (i) a breach of any of the Indemnifying Party's warranties, representations or other obligations in this MTA, or (ii) gross negligence or willful misconduct on the part of the Indemnifying Party, except to the extent such claim or claims arise from the gross negligence, or willful misconduct of the other Party or any breach of any representation or warranty of the other Party made pursuant to this Agreement.

5.3. In all cases where one Party seeks indemnification by the other under Section 5.2, the Party seeking indemnification shall promptly notify the Indemnifying Party of receipt of any claim covered by such indemnification obligation.

5.4. In no event shall Provider, its directors, personnel and its subsidiaries be liable for any use, storage and disposal of the Material by HUB.

5.5. The Parties agree that, in no event, any Party (including its affiliates and subcontractors, and their respective directors, officers, and employees) shall be liable for any indirect, special, consequential, incidental, punitive or non-contractual damages (including without limitation damages for lost profits, loss of revenue and loss of business opportunities) arising out of or related to this MTA.

5.6. Notwithstanding anything herein to the contrary and to the maximum extent as permitted by law, the total aggregate liability of HUB to Provider, on all claims of any kind, whether in contract, tort or strict liability, arising out of the performance or breach of this Agreement shall be limited to the amount actually paid by the insurance company of HUB. HUB shall provide the applicable insurance policy upon request. The foregoing limitation shall not apply to any obligations arising out of in connection with willful misconduct on the part of HUB.

6. MISCELLANEOUS

6.1. This MTA may not be transferred or assigned in any form by either Party without the prior written consent of the other Party. Any permitted assignment shall be binding on the successors of the assigning Party. Any unauthorized transfer or assignment shall be void.

6.2. No modification or addition to this Agreement shall be binding on either Party unless reduced to writing and signed by all Parties.

6.3. Consent by either Party to, or waiver of, a breach by the other Party, whether express or implied, shall not constitute consent to, waiver of, or excuse for any other different or subsequent breach.

6.4. This Agreement shall be governed by and construed in accordance with the law of the Czech republicwithout regards for the conflicts of laws principles thereof. All disputes arising in connection with the present agreement, or further agreements resulting therefrom, shall be submitted to the exclusive jurisdiction of the competent courts in Czech republic.

6.5. This agreement is executed in 2 counterparts, one for each of the Party.

IN WITNESS WHEREOF, the Parties have executed, or have caused their authorized representatives to execute this MTA as of the date last written below:

Stichting Hubrecht Organoid Technology:

By: Rob Vries

Title: COO

Date: 17.11.2018

Fakultní nemocnice v Motole

Title: director

Date: 26. 11. 2018