**FOR THE PERFORMANCE OF A STUDY**

**PROTOCOL ACRONYM FENICE II**

**PROTOCOL TITLE Fluid challenge in Intensive Care: a worldwide global**

**inception cohort study.**

**This Agreement is entered into by and between**

**IRCCS HUMANITAS MIRASOLE S.P.A.** with registered office at Rozzano, Via A. Manzoni n. 56

Fiscal Code 10125410158, VAT IT10982360967 duly represented by the Chief Executive Officer Dr. Luciano Ravera (to follow “**HUMANITAS**”)

AND

**ORGANIZATION NAME:** ………………………………

with registered office at: ………………………………

Fiscal Code and VAT: ………………………………

duly represented by: ………………………………

(to follow, “the Participating Center”)

HUMANITAS and ………………………………

are herein collectively referred as the “Parties”, and individually as “Party”.

**WHEREAS**

A) HUMANITAS is a renown center of excellence for research and treatment of a wide range of

disease, including a noted Intensive Care Department, and acknowledged by the Italian Ministry

of Health as a Clinical Research Institute (IRCCS);

B) HUMANITAS has taken the initiative to develop and sponsor a clinical study in the field of theIntensive Care, aimed at exploring relationship and impacts of the modality of fluid

administration on clinical outcomes of critically ill patients; the Study, described in the Protocol,

will be commonly referred to in this Agreement as “Study”;

C) HUMANITAS shall act worldwide as the non-commercial legal responsible (sponsor) for the

Study in the framework of this Agreement.

D) The Participating Center, represented by its legal representative co-signer of this contract, has

facilities and personnel with requisite skills, experience, and knowledge to participate in the Study

in accordance with this Agreement, the Study protocol including any amendments (attached as

**Annex 1** to this Agreement – the “**Protocol**”).

**1. AS USED IN THIS AGREEMENT, THE FOLLOWING TERMS SHALL HAVE THE MEANINGS SET**

**FORTH BELOW:**

**“Agreement”:** the present research agreement, its appended documents and all amendment hereafter signed by the Parties being an integral part of said agreement.

**“Case Report Forms” or “CRFs”:** shall mean the Case Report Form which is a printed, optical or electronic document designed to record all of the Study required information which

shall be reported to HUMANITAS on each patient (Study Subject).

**“Data Base”:** the electronic medium used by HUMANITAS (RedCap) for the needs of the Study and containing all information relating to the Study.

**“Study Subject”:** patients selected to be enrolled in the Study, in accordance with, and who meet, the eligibility criteria specified in the Protocol.

**“Ethics Committee”:** shall mean the ethics committee(s) established pursuant to local legal and regulatory requirements for the purpose of reviewing and/or approving clinical

investigations.

**“Legal responsible”:** HUMANITAS is the entity which takes the full responsibility for the initiation and management of this study following the Protocol in accordance with the legal and

regulatory requirements.

**“Legal representative”:** person at participating institution with legal rights for signing the Agreement.

**“Study Steering Committee”:** the related reaserach committee, as described in the Protocol.

**Now therefore, the Parties agree as follows:**

**2. SCOPE OF AGREEMENT**

2.1. The Agreement intends to determine the conditions for the initiation, performance and

termination of the Study to be conducted by the Participating Center pursuant to the Protocol.

The Annexes, including any amendments, constitute an integral part of this Agreement.

2.2. In case of any inconsistency between the terms and conditions of this Agreement and those

contained in the Protocol, the terms and conditions of this Agreement shall prevail except with

respect to medical, scientific or clinical matters for which the provision of the Protocol shall take

precedence.

**3. CONFORMANCE WITH LAW AND ACCEPTED PRACTICE**

3.1. HUMANITAS shall coordinate the Study between the different participating centers.

3.2. The Parties agree that the Study will be performed in accordance to:

- the Declaration of the Helsinki World Medical Association Recommendations Guiding

Physicians in Biomedical Research Involving Human Subjects including amendments

thereto;

- the "ICH Harmonised Tripartite Guideline, Guideline for Good Clinical Practice" and the

"Notes for Guidance on Good Clinical Practice" CPMP/ICH/135/95;

- the Regulation (EU) 2016/679 of the European Parliament and of the Council of 27 April

2016 on the protection of natural persons with regard to the processing of personal data and

on the free movement of such data (General Data Protection Regulation or “GDPR”);

- all applicable national laws and regulations;

- the Protocol and its amendments;

- any specific Study instructions issued by HUMANITAS;

- any other pertinent rules and regulations, if applicable.

**4. PERIOD OF PERFORMANCE**

4.1. The Study is expected to start in January 2024 and will enroll Study Subjects according to the

enrolling periods defined in the Protocol.

**5. FINANCIAL COMPENSATION**

5.1. No payments shall be made by HUMANITAS to the Participating Center.

**6. OBLIGATIONS OF PARTICIPATING CENTER**

6.1. The Legal representative of the Participating Center authorizes the performance of the Study in its Participating Center and will ensure that the personnel (including investigator(s)) who

participate in the conduct of the Study is informed of and abide by all applicable terms of this

Agreement.

6.2. Participating Center shall only enroll patients in Study, as per eligibility criteria of the Protocol.

6.3. In the event that Participating Center shall no longer be interested in or be unable to enroll new Subjects in Study, the Participating Center will ensure that data for the already enrolled Study

Subjects shall be provided as per Protocol.

6.4. Participating Center shall not document or subcontract any third party without prior approval

of HUMANITAS. Notwithstanding HUMANITAS’s approval for the delegation, Participating

Center shall remain liable to HUMANITAS. Any agreement with sub-contractors shall reflect

the terms of this Agreement.

6.5. Participating Center is responsible for the conduct and supervision of the Study, including the

Study Subjects and only after all necessary legal, regulatory or other approvals have been granted

including, without limitation, those of any Institutional Review Board/Independent Ethics

Committees and strictly in accordance with the terms of any such approval.

6.6. Participating Center shall not make any changes to the Protocol without the approvals of

HUMANITAS and/or Ethics Committees.

6.7. Prior to the Study Subject’s enrolment into the Study, the Participating Center shall obtain the Study Subjects' express, written, dated and signed informed consent to the collection,

confidential disclosure, processing and transfer of the Study Subject’s health and personal data

to HUMANITAS, in accordance with local regulation and the European Regulation on General

Data Protection 2016/679 (“GDPR).

6.8. The Participating Center further agrees as follows:

• ensure that there is no transfer of any data relating to individuals other than the

categories of data specified in the Protocol for the purpose of this Study;

• ensure that Study Subject data (including responses to queries) will be transferred to

HUMANITAS in a coded form and in a timely manner, through reporting on the

electronic CRFs specifically designed by HUMANITAS for this Study and trough the

encypted channes provided by the software platform RedCap.

6.10 Participating Center shall set-up an investigator file to maintain all Study-related documents. The files must be kept in a secure locationfor the duration of the study and archived after completion or premature termination of the study in a secure facility for 5 years after the sudy termination.

Participating Center shall not destroy those documents without prior written consent from

HUMANITAS.

**7. OBLIGATIONS OF HUMANITAS**

7.1. HUMANITAS shall take responsibility for the initiation and management of the Study,

following the Protocol, in accordance with all applicable legal and regulatory requirements;

7.2. HUMANITAS shall be responsible for the development of the Protocol as well as all eventual amendments to this Protocol.

7.3. HUMANITAS shall ensure that a Study Steering Committee, and any other committee as

defined in the Protocol (i.e cohort specific committees), are in place for the governance of Study.

7.4. HUMANITAS shall be responsible for the distribution of the Protocol (initial and amended

versions) and all Study related documents (understood as CRFs, guidelines etc., the list not being

exclusive) to the Participating Center.

7.5. HUMANITAS shall be responsible for the central data management of the Study including the collection and analysis of the Study data and its inclusion in the Study database.

7.6. Upon receipt of all the study-related documents and regulatory approvals HUMANITAS will

give the final authorisation to Participating Center for participation to Study, as defined in the

Protocol.

7.7. HUMANITAS shall provide the Participating Center with the following:

- the Protocol and any applicable amendment;

- a copy of the opinion of the Ethics Committee;

- a copy of the approved Patient Information sheet and data protection notice.

**8. DATA PROTECTION**

8.1. The Participating Site and Sponsor are considered independent controllers for the Processing of the Personal Data and will both handle all Personal Data in accordance with the EU Regulation 2016/679 (GDPR) for the performance of the study.

8.2. In Processing Personal Data, the Parties shall:

i. only Process Personal Data in accordance with this Agreement;

ii. not process or aggregate Personal Data for purposes other than as per this Agreement;

iii. only appoint Data Processors that enter into a written and enforceable agreement with

obligations compliant to art. 28 of the GDPR;

iv. (wherever possible, notify the other party promptly in writing before complying with any

Personal Data disclosure request in connection with this Agreement by a government

entity, data subject, organization or other entity;

v. partner with the other party in responding to any requests from an individual to exercise

their rights under applicable privacy and data protection law, and any other inquiry from

an individual, regulatory or other third party in connection with this Agreement;

vi. reasonably assist each other to respond to audit requests and execute any findings from

the audit related to this Agreement;

vii. implement and maintain adequate technical, organizational, administrative, and physical

practices regarding security, confidentiality, integrity, availability, backup, and disaster recovery

protection that are consistent with leading industry standards and practices and to protect against known risks and vulnerabilities when handling Personal Data;

viii. and if Participating Site or Sponsor suspect or become aware of an Incident:

1) comply with notification, investigation and corrective action requirements within 72

hours to allow time to comply with Applicable Law;

2) not reference the other party in any public announcements relating to such Incident

without prior written approval if reasonable; and

3) take reasonable steps to remediate and prevent a recurrence of such Incident.

ix. Art. 82 GDPR shall remain unaffected. No parts of the study or the Agreement justify

any claim by data subjects or other third parties, nor shall it constitute a joint or several

liability of the parties. Each party shall be liable to the other party for the damages

including fines caused by the Processing for which it is responsible.

**9. INTELLECTUAL PROPERTY**

9.1 Each Party remains the sole owner of its Background Intellectual Property (Background IP). To the extent necessary for the performance of the Study and to the extent that a Party is legally able to do so, each Party participating in the Study will grant the other Parties and any third parties participating in the Study a royalty-free, non-exclusive, non-transferable license to use its

Background IP for the purpose of carrying out the Study, but for no other purposes.

9.2 With the exception of personal and confidential medical records, the sole and exclusive right to any data, inventions, discoveries or innovations, whether patentable or not, and all Foreground

Intellectual Property, arising directly or indirectly in the performance of the Protocol and Study

(the “IPRs”) shall vest in HUMANITAS. The Participating Center will provide to HUMANITAS

in writing any such IPRs.

**10. CONFIDENTIALITY**

10.1. The Agreement and the terms and conditions hereof and any and all other information related to the Study shall be confidential (“Confidential Information”) and none of the Parties shall, without the prior written permission of the disclosing Party, disclose the same to any third

party except for the specific and limited purposes set forth under this Agreement or if required

by applicable law and regulations.

10.2. The provisions of paragraph 9.1 shall not apply to:

- any of the Confidential Information which at the time of receipt by the receiving Party is in

the public domain;

- any of the Confidential Information which after its receipt by the receiving Party is made

public by a third party acting without impropriety in so doing;

- any of the Confidential Information which the receiving Party can establish was in its

possession before receipt from the disclosing Party or was developed independently or

acquired directly or indirectly from a source wholly independent of the disclosing Party;

- any reference to the Study made by the Participating Centre in the report of its/his activities,

that is requested by competent Authorities.

- any of the Confidential Information whose disclosure is required by applicable laws,

regulations or by final judicial decision to be disclosed. The Participating Center shall inform

promptly the HUMANITAS and disclose only the Confidential Information required by the

applicable laws, regulations or final judicial decision.

10.3. The terms and conditions of these obligations of confidentiality and restricted use contained

herein are applicable during the term of the Agreement and shall survive ten (10) years from

its date of termination, whether by expiration or by earlier termination.

**11. MONITORING/AUDIT/INSPECTION**

11.1. Monitoring

Although not foreseen upfront, the Participating Center shall permit monitoring visits by

HUMANITAS and/or any HUMANITAS sub-contractor. The Participating Center hereby

allow HUMANITAS and/or any HUMANITAS sub-contractor to monitor the facilities and

all related documents being used for the Study. Monitoring visits will be during normal

working hours and days, according to the monitoring plan. Monitoring visits will be carried

out by duly appointed clinical monitors. The Participating Center will ensure that the monitor

has access to the full medical records of the patients (either paper or electronic).

11.2. Audit

The Participating Center hereby allow HUMANITAS and/or any HUMANITAS subcontractor

to audit the facilities (including approved subsites if applicable) and all related

documents being used for the Study. The Participating Center will be notified at least three

(3) weeks in advance.

11.3. Inspection

The Participating Center hereby allow any Competent Health Authorities and to inspect the

facilities (including approved subsites if applicable) and all related documents being used for

the Study. The Participating Center shall inform HUMANITAS within 24 hours if any Competent Health Authorities want to inspect and audit the facilities and all related documents being used for the Study.

**12. STUDY DATA AND REPORTING**

12.1. HUMANITAS shall centrally manage all data relating to the Study (“Study Data”); including

the collection and analysis of the Study Data from cohorts and their inclusion in the

HUMANITAS database.

12.2. HUMANITAS is the owner of the Study database and of the results.

**13. PUBLICATION**

13.1. The results of all HUMANITAS studies are published, irrespective of the findings (both

positive and negative, statistically significant or not), under the responsbaiity of HUMANITAS

Principal Investigator.

13.2. Prior to submission, all publications (e.g. papers, abstracts, presentations) including any Study Data will be submitted for review and approval by the Study Steering Committee. The

authorship rules are described in the Protocol.

13.3. Participating Center shall have a non-exclusive right to use Study results for teaching and for

non-commercial research purposes only.

**14. TERM AND TERMINATION OF AGREEMENT**

14.1. This Agreement and Participating Center’s obligations shall enter into force as of the last dateof signature (“Effective Date”).

14.2. This Agreement shall remain in force and effect for the duration of the Study as described in

the Protocol unless terminated earlier in accordance with this Article 14.

14.3. Each Party may terminate this Agreement immediately if the other Party commits a breach of this Agreement, which, in the case of a breach capable of remedy, shall not have been remedied within sixty (60) days of the receipt to the Party in default of a written notice identifying the breach and requiring its remedy. It is expected that such notice to terminate this Agreement

shall not be issued until the matter in question has been raised in writing and discussed during

the above mentioned sixty (60)-day period.

14.4. Notwithstanding this Article 14, the Agreement may be terminated earlier by HUMANITAS, in accordance with terms described in the Protocol;

14.5. Articles 8, 9, 10, 11, 12 and 13 of this Agreement shall remain in force after termination of this Agreement.

**15. NOTICES AND ADMINISTRATIVE / LEGAL CONTACT PERSONS**

15.1. If not explicitly stated in this Agreement that a notice shall be in writing, any notices, requests, consents and other communications to be given by a Party under this Agreement may also be executed by email.

15.2. Notices in writing shall be deemed to be valid and effective if the notice

i) has been personally served,

ii) sent by registered prepaid airmail, or

iii) sent by recorded delivery mail to the representatives of the Parties at their addresses

mentioned herein.

15.3. Notices by email shall be deemed to be valid and effective if sent to representatives of the

Parties at the addresses as listed herein and if delivery was recorded and a transmission report

has been received by the sender.

15.4. The names and contact details of the administrative / legal contact persons are indicated below:

|  |  |
| --- | --- |
| HUMANITAS | **Participating Center** |
| IRCCS Istituto Clinico Humanitas -  Humanitas Mirasole S.p.A  Via Alessandro Manzoni, 56  Rozzano (MI) - Italy  c.a. Prof. Maurizio Cecconi  Dr. Antonio Messina |  |

**16. DECLARATIONS**

16.1. For the purposes of this Section 16, “Debarred or Disqualified Person” means any person

subject to limitations or any form of enforcement imposed upon clinical Investigators or

clinical study sites by the United States Food and Drug Administration (FDA), the European

Medicines Agency (EMA), or any regulatory authority or other recognized national, multinational,

or industry body.

16.2. The Participating Center declares that investigators, or any member of its personnel, has ever been and is not currently a Debarred or Disqualified Person, nor will the Participating Center employ any Debarred or Disqualified Person or have engaged in any conduct or activity that could render any of them a Debarred or Disqualified Person and that it has no notice that the FDA, the EMA or other regulatory authority intends to seek disqualification or debarment. If

during the term of this Agreement, the Participating Center, or any member of its personnel

(i) comes under investigation by FDA, the EMA or other regulatory authority for debarment

action or disqualification, (ii) is debarred or disqualified, or (iii) engages in any conduct or

activity which could lead to any of them being rendered a Debarred or Disqualified Person,

the Participating Center will immediately notify HUMANITAS.

16.3. The Participating Center declare that each has disclosed and agrees to disclose any conflict of interest in compliance with HUMANITAS policy related to Conflict of Interest described in the Protocol. The Participating Center, investigator or member of its personnel will comply

with all other disclosure requirements of any regulatory authority or other governmental agency

related to conflicts of interest.

**17. GOVERNING LAW AND COMPETENT JURISDICTION**

17.1. This Agreement shall be governed by and construed in accordance with the laws of Italy. The parties agree that in case of dispute which is not amicably resolved, the decision is taken by the courts of Milan.

17.2. If any provision of this Agreement is determined to be invalid or void, the remaining provisions shall remain in effect. In such a case the invalid provision will be replaced by a provision being legally acceptable and in compliance with the objective of the invalide provision.

17.3. This Agreement and all attachments hereto constitute the entire Agreement between the Parties with respect to the subject matter included herein and no variation, modification or waiver of any terms or conditions hereof shall be deemed valid unless made in writing and signed by the Parties hereto. This Agreement supersedes any and all prior agreements and understandings, whether oral or written, between the parties with respect to the subject matter included herein.

**18. ANNEXES**

The documents enumerated hereafter are understood to form an integrated part of this Agreement:

Annex 1 – Protocol

This Agreement may be executed in two or more counterparts, each of which shall be deemed an original, but all of which taken together shall constitute one and the same instrument. Signatures to this Agreement transmitted by email, portable document format (or .pdf), or by any other electronic means intended to preserve the original graphic and pictorial appearance of this Agreement shall have the same effect as the physical delivery of the paper document bearing original signature.

**IN WITNESS WHEREOF, the Parties hereto have caused this Agreement to be duly executed as of the Effective Date**

|  |  |
| --- | --- |
| **For and on Behalf of HUMANITAS**  NAME: Dr. Luciano Ravera  TITLE: Legal Representative -  Chief Executive Officer  DATE:  SIGNATURE : | **For and on Behalf of the Participating**  **Center**  NAME:  TITLE: Legal Representative -  Chief Executive Officer  DATE:  SIGNATURE : |