



MICROB·AI·OME

Federated artificial intelligence for privacy-preserving international stratification of colorectal cancer patients

Study Initiation Package

December 21st, 2023

Microb-AI-ome - Public deliverable report **Deliverable 2.2**

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This report is published on the Microb-AI-ome website www.microbaiome.net

1 Microb-AI-ome as a whole

What is Microb-AI-ome's goal?

Colorectal cancer (CRC) is the 2nd most common type of cancer in the world (WHO Global Health Estimates 2019). However, identifying CRC early improves disease prognoses, and as such lessens the disease burden on the individual and on society as a whole. Current CRC screening programs utilize a quantitative faecal immunological test (FIT) to predict the need for colonoscopy for the detection of colorectal lesions indicative of CRC. However, the FIT has a high false-positive rate of over 37% leading to many unnecessary, unpleasant, invasive and costly colonoscopies. Microb-AI-ome aims to reduce this false-positive rate by 20% points by utilizing powerful information hidden in our stool microbiomes.

What is Microb-AI-ome's approach?

Artificial intelligence (AI) and machine learning (ML) technology have started to pave the way towards highly personalized medicine. However, while the number of identified associations between microbiome profiles and CRC has been rising in recent years, robust AI models for personalized prediction of a need for a colonoscopy are still missing. The big data needed to train such models is distributed over many repositories around the globe, and privacy regulations are hindering its effective integration. With Microb-AI-ome, we will overcome this barrier by establishing the first privacy-preserving federated big data network for CRC research. We will integrate isolated, national databases, into one international federated database network - rather than a cloud - covering metagenomes for over 4,000 individuals screened for CRC, and an expected total of 100,000 by 2026. Microb-AI-ome ensures that no sensitive patient data will leave the safe harbours of the local databases while still allowing for the training of robust AI models, which we will demonstrate in clinical practice allowing regulatory bodies to adopt evidence-based guidelines.

2 Study Initiation Package

2.1 Rational

The Microb-AI-ome clinical partners comprise four expert centers for CRC screening: three in Ireland (MMUH, SVUH and Mercy Cork) and AHPH in France. During the course of the Microb-AI-ome project, the partners will screen >5,000 individuals during national CRC screening programs and population screening that will be utilized for CRC Stratifier evaluation. This study aims to determine if using AI to analyse the complex gut microbiome can provide a more accurate CRC screening method and hence improve survival from this disease.

2.2 Description

The proposal exploits the clinical, laboratory and data analysis (AI) expertise of three EU countries and is now at an advanced stage of development to commence the study. Outlined below, in summary form, are the specific goals achieved to implement clinical and initial data capture component of the proposed study.

In brief:

- a. The clinical sites have been chosen in Ireland and France.

- b. Clinical leads have been established and study nurses are being recruited. Hospital/academic management support has been confirmed in the Irish sites.
- c. IT equipment, including specific servers, together with IT support in each clinical site have been identified and purchased.
- d. Protocols for patient recruitment, clinical, colonoscopy and pathology data capture agreed as well as stool sample collection, storage and transfer to laboratory for microbiome analysis.
- e. Nutritional/dietary questionnaires have been agreed between Irish and French clinical centres.
- f. Ethics submissions are complete and have been formally approved in all 3 Irish centres (appendix 1).
- g. Ethic submissions are complete and have been formally approved in France (appendix 2). The ClinicalTrials.gov identifier is NCT06174233.
- h. Administrative support with responsibility for budget allocation, audit of activity, organisation of and monitoring of project targets has been arranged (within MMUH) in Ireland, with the appointment of an Irish study coordinator with extensive experience in both clinical studies and data governance. Similar arrangements are being put in place in France.
- i. Data processing and governance structures have been decided on (appendices 3 & 4).
- j. All subcontract/service level agreements within Ireland incorporating data sharing protocols are complete (appendix 5).

2.3 Microb-AI-ome partners involved

▪ Main researchers

The Microb-AI-ome consortium consists of the following eight partners:

1. **Universitaet Hamburg** (UHAM), Germany (coordinating institution)
2. **UNIVERSITY COLLEGE CORK - NATIONAL UNIVERSITY OF IRELAND, CORK** (UCC), Ireland
3. **GNOME DESIGN SRL** (GND), Romania
4. **tp21 GmbH** (TP21), Germany
5. **RESEARCH INSTITUTE AG & CO KG** (RI), Austria
6. **INSTITUT NATIONAL DE RECHERCHE POUR L'AGRICULTURE, L'ALIMENTATION ET L'ENVIRONNEMENT** (INRAE), France
7. **ASSISTANCE PUBLIQUE HOPITAUX DE PARIS** (APHP), France
8. **MATER MISERICORDIAE UNIVERSITY HOSPITAL** (MMUH), Ireland

▪ Collaborating researchers¹

1. Mercy University Hospital (Cork, Ireland)
2. St. Vincents University Hospital (Dublin, Ireland)
3. MMUH Gastrointestinal Unit (Dublin, Ireland)
4. Hopital Avicenne (Bobigny, France)
5. Institut Arnault Tzanck (Mougins, France)
6. Hopital Jean Mermoz (Lyon, France)
7. Hopital Cochin (Paris, France)
8. Centre hospitalier de Meaux (Meaux, France)
9. Clinique du Palais (Grasse, France)

¹ See in total: CESSDA list of Data Management Questions (2019), CESSDA Training Team (2017 - 2022). CESSDA Data Management Expert Guide. Bergen, Norway: CESSDA ERIC. Retrieved from <https://dmeg.cessda.eu/>, p 1.

10. Clinique de Bercy (Charenton-le-pont, France)
11. Clinique Belharra (Bayonne, France)
12. Hopital Louis Pasteur (Le Coudray, France)
13. Hopital Edouart Herriot (Lyon, France)
14. CHU Dupuytren (Limoges, France)
15. CHU Villeneuve Saint Georges (Villeneuve Saint Georges, France)
16. CHI de Créteil (Créteil, France)
17. GHI Le Raincy Montfermeil (Montfermeil, France)
18. Centre hospitalier Saint Malo (Saint Malo, France)
19. CHG Henri Duffaut (Avignon, France)
20. Hopital De la Fontaine-Saint Denis (Saint Denis, France)
21. Centre hospitalier Bretagne Atlantique (Vannes, France)
22. Hopital Jacques Monod Le Havre (Montivilliers, France)
23. Centre Hospitalier de Cholet (Cholet, France)
24. CH Perpignan (Perpignan, France)
25. CHI Aix-en-Provence (Aix-en-Provence, France)

3. Conclusion, next steps

With the steps outlined above, it is anticipated that patient recruitment can commence in one Irish centre within the next month, followed shortly by the remaining two Irish clinical sites. The French site initiation is planned to follow shortly as well.

4. Annexes

Appendix 1 – Formal ethics approval from Irish clinical sites.

Appendix 2 – Formal ethics approval from French clinical sites.

Appendix 3 – Diagrammatic representation of data capture, processing, flow and governance (Ireland).

Appendix 4 – Diagrammatic representation of data capture, processing, flow and governance (France).

Appendix 5 – Service level agreements within Ireland (incorporating data governance).

Appendix 1 – Formal ethics approval from Irish clinical sites.

COISTE EITICE UM THAIGHDE CLINICIÚIL
Clinical Research Ethics Committee of the Cork Teaching Hospitals

Tel: +353-21-4901901

Email: crec@ucc.ie

University College Cork
Lancaster Hall
6 Little Hanover Street
Cork
Ireland

**CREC Review Reference Number: ECM 4 (ii) 20/06/2023
& ECM 5 (10) 20/06/2023 & ECM 3 (u) 24/10/2023**

Date: 26th September 2023

Professor Micheal O'Riordain
Clinical Professor of Surgery
Department of Surgery
Mercy University Hospital
Cork

Study Title: Federated artificial intelligence for privacy-preserving international stratification of colorectal cancer patients.

Dear Professor O'Riordain

The following document has been noted and filed:

- Proof of data protection officer approval dated 22nd September 2023.

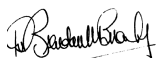
Full approval is now granted to carry out the above study. The date of this letter is the date of authorization of the study.

Please keep a copy of this signed approval letter in your study master file for audit purposes. The study must be carried out in accordance with General Data Protection Regulation and Health Research Regulation 2018/2021.

You should note that ethical approval will lapse if you do not adhere to the following conditions:

1. Submission of an Annual Progress Report/Annual Renewal Survey (due annually from the date of this approval letter). **We would encourage you to keep note of this date as the CREC will not issue a reminder.**
2. Report unexpected adverse events, serious adverse events or any event that may affect ethical acceptability of the study
3. Submit any change to study documentation (minor or major) to CREC for review and approval. Amendments must be submitted on an amendment application form and revised study documents must clearly highlight the changes and contain a new version number and date. Amendments cannot be implemented without written approval from CREC.
4. Notify CREC of discontinuation of the study
5. Submit an End of Trial Declaration Form and Final Study Report/Study Synopsis when the study has been completed.

Yours sincerely



Professor Brendan Buckley
Vice Chairman
Clinical Research Ethics Committee
of the Cork Teaching Hospitals

The Clinical Research Ethics Committee of the Cork Teaching Hospitals, UCC, is a recognised Ethics Committee under Regulation 7 of the European Communities (Clinical Trials on Medicinal Products for Human Use) Regulations 2004, and is authorised by the Department of Health and Children to carry out the ethical review of clinical trials of investigational medicinal products. The Committee is fully compliant with the Regulations as they relate to Ethics Committees and the conditions and principles of Good Clinical Practice.

Professor Glen Doherty
Consultant Gastroenterologist
St. Vincent's University Hospital
Elm Park
Dublin 4.

16th November 2023

Ref No: RS23-057

Study Title: Federated artificial intelligence for privacy-preserving international stratification of colorectal cancer patients


Documents: CV_MOR; GD GCP October 2020; GD signed CV Nov 2022; REC Checklist; REC Cover Letter; SVUH Protocol Microbiome V1.0 25JUL2023; SVUH Research-Study-Registration-Form-2022; SVUH PIL Microbiome V2.0 14_SEP_2023 (1); SVUH-REC-Application form Microbiome Study_26.10.23; Revisions Cover letter Microbiome;

Dear Professor Glen Doherty,

Following review of the responses and clarifications received, this study has been granted full Ethics approval.

Please note, it is the responsibility of the Principal Investigator to retain full file copies of all documentation submitted and received in respect of this application.

Yours sincerely,



Professor Carel Le Roux
Chairperson
SVHG Research Ethics Committee



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Ospidéal Ollscoile

Mater Misericordiae

Siúracha na Trócaire

Sráid Eccles, Baile Átha Cliath D07 R2WY, Éire

Web: www.mater.ie



Not for prescription purposes

Dr. Jan Leyden
Consultant Gastroenterologist
Mater Misericordiae University Hospital
Eccles Street
Dublin 7

18th December 2023

Institutional Review Board Reference: 1/378/2378

RE: **Microb-AI-ome – Federated artificial intelligence for privacy-preserving international stratification of colorectal cancer patients**
MMUH Data Protection Impact Assessment
Participant Information Leaflet (Version 2, December 2023)
Consent Form (Version 2, December 2023)
Standard Application Form (Version 2, 12th October 2023)
Protocol (Version 1.0, 12th June 2023)
Narrative Summary (Version 1.0, 12th June 2023)

Dear Dr. Leyden,

I acknowledge receipt of your correspondence dated 14th December 2023 enclosing the following documentation for the above research study to be carried out at the Mater Misericordiae University Hospital (MMUH).

1. Cover Letter (14th December 2023)
2. Standard Application Form (Version 2, 12th October 2023)
3. Curriculum Vitae for Prof. Brendan Kinsley, Ms. Erin Daly & Ms. Mary Carey
4. Prof. Paul W. O'Toole correspondence (28th August, 6th November, 6th December, 7th December & 12th December 2023)
5. Email correspondence with Ms. Anna Broderick (12th December 2023)
6. Participant Information Leaflet (Version 2, December 2023)
7. Consent Form (Version 2, December 2023)
8. Budget Breakdown
9. IT email correspondence (3rd August & 01st December 2023)

This correspondence has been noted and approval for this research study to proceed at MMUH is granted.

Please note the following provisions:

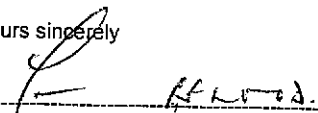
1. Amend the PIL & CF to clearly state Version 2, December 2023 as amendments have been made to the original documents.
2. Once the agreements have been finalised, submit the partially executed agreements to Ms. Hannah King, REC Administrator for CEO signature. **No sharing/processing of data etc. can occur until agreements are finalised.**

It is your responsibility to adhere to the approved research protocol and ensure the following:

1. Only Investigators named on the approved IRB application form are involved in the research;
2. All investigators involved with the research only use the approved documents without deviation (unless they have been approved by the IRB);
3. To submit annual reports setting out the progress of the research;
4. To notify the IRB when the research is concluded.

It is your responsibility to comply with your legal obligations under Data Protection Law and the Health Research Regulations. You should consult with the research study site Data Protection Officer on any data protection issues in particular in relation to the sharing of any personal data outside of the MMUH. Detailed GDPR Guidance for research is available on the HRB website: <https://www.hrb.ie/funding/gdpr-guidance-forresearchers/>.

Yours sincerely


Dr. Georgina Flood
Chairperson
Institutional Review Board

Cc: Prof. Padraic MacMathuna, Clinical Director, The National Bowel Screening Programme.
Cc: Prof. Brendan Kinsley, Consultant Endocrinologist and Clinical Director of the DERI Directorate, MMUH
Cc: Ms. Erin Daly, Operations Manager of the DERI Directorate, MMUH

'Commitment to Excellence'

Chairman: Mr David Begg Vice Chair: Mr David O'Kelly CEO: Mr Alan Sharp

Directors: Mr Rod Ensor, Prof Cecily Kelleher, Dr Mary McMenamin,

Dr Brian Marsh, Ms Ellis O'Brien, Ms Brid Cosgrove, Ms Suzanne Dempsey, Prof Jim Egan, Ms Anne Vaughan, Mr Pat O'Doherty

Appendix 2 – Formal ethics approval from French clinical sites.

Comité de protection des personnes Sud-Est IV

Avis sur une demande initiale

CPP

Nom du CPP : Comité de protection des personnes Sud-Est IV
Adresse : Centre Léon Bérard - 28 rue Laennec 69373 LYON CEDEX 08 France
Courriel : Centre Léon Bérard - 28 rue Laennec 69373 LYON CEDEX 08 France
Téléphone : 0478782761

Promoteur / Demandeur

Promoteur : inrae
Représentant légal (UE) : -
Mandataire : -

Dossier

Numéro SI : 23.03341.000174
Numéro national : 2023-A01941-44
Référence interne : INRAE-MGP-2023-02

Règlementation : Loi Jardé
Qualification : Catégorie 3 questionnaire

Produit ou acte : Hors produits de santé (produits non mentionnés à l'article L.5311-11 du code de la santé publique)

Investigateur : Robert Benamouzig
Titre : « Apport de l'analyse métagénomique du microbiote fécal combiné à l'intelligence artificielle pour la prédiction du risque de cancer colorectal » Etude chez des patients devant bénéficier d'une coloscopie
Acronyme : « Le French Gut-colo »

Date de réception : 25 septembre 2023 et compléments le 03 octobre 2023

Ce dossier a été étudié en séance le 24/10/2023. Au vu des réponses obtenues, l'avis suivant a donc été émis. Cet avis court à compter du changement de statut sur le SI.

Considérant que les conditions éthiques sont remplies notamment au regard des éléments de l'article L.1123-7 du code de la santé publique, l'examen du comité permet de conclure que la recherche peut être réalisée et de rendre l'avis suivant :

Avis favorable

Cet avis est valable deux ans. Conformément à l'article L.1123-11 du code de la santé publique, le promoteur doit déclarer au CPP le début de la recherche. Cette déclaration se fait directement sur le SIRIPH2G (bouton "démarrer l'étude").

Si vous n'avez pas été en mesure d'inclure un premier participant à la recherche dans ce délai, vous pouvez demander au CPP une prorogation de cet avis avant la fin de validité de ce dernier (article R.1123-26 du code de la santé publique).

Transmettre pour information et lors de la prochaine MS :

- Les BPC du Dr CHERON et du Dr DELASALLE (datant de moins de 3 ans)
- Le CV du Dr LEFORT avec son numéro RPPS

Personnes ayant délibéré

Collège	Catégorie	Nom et prénom
Collège I	Qualification RIPH - Biostatistique ou épidémiologie	N. FALETTE
	Qualification RIPH - Biostatistique ou épidémiologie	P. CONY-MAKHOUL
	Qualification RIPH - Autre	M. MONTANGE
	Qualification RIPH - Autre	R. MARAVAL-GAGET
	Qualification RIPH - Autre	A. BERTRAND REYNAUD
	Pharmacien hospitalier	M. PHILIPPE
	Auxiliaire médical	S. BOUVET
	Auxiliaire médical	G. DUYCK
Collège II	Compétence éthique	D. SALAKO
	Compétence en sciences humaines et sociales ou action sociale	V. BAUDRY
	Compétence en sciences humaines et sociales ou action sociale	Y. DA CRUZ
	Compétence juridique	B. BENAÏSSA
	Compétence juridique	E. CHAPOUTIER
	Compétence juridique	M-A. EUDELINÉ
	Représentant d'association agréée	O. BONNET
	Représentant d'association agréée	J. SASSARD
Représentant d'association agréée	P. CHEMLI	

Documents analysés par le CPP

Annexe	N° version	Date (jj/mm/aaaa)
Document attestant que la recherche est conçue et réalisée conformément aux dispositions législatives et réglementaires du titre II du Code de la Santé Publique		14/09/2023
Courrier de réponse à la délibération A23-241		21/11/2023
Résumé du protocole en français (selon arrêté du 21 décembre 2018) *	1	21/11/2023
- Document(s) d'information*	2	15/11/2023
- Questionnaire(s) et/ou trame entretien(s)	1	13/09/2023
Autre(s) document(s) transmis par le promoteur :		
- Protocole de la recherche*	1	21/11/2023
- Dépliant d'aide au recrutement		Non daté
- Déclaration intérêt recherche		14/09/2023
- Traitement des données	1	02/10/2023

- Liste investigateurs (20 investigateurs / 20 centres dont coordonnateur)		21/11/2023
- CV des investigateurs		2022-2023

**Document(s) transmis en version suivi de modification et finale*

La Présidente, Dr Amandine BERTRAND

Appendix 3 – Diagrammatic representation of data capture, processing, flow and governance (Ireland).

Step 3
Each site will independently send model parameters to UHAM.

UHAM will not have access to any personal data.

UHAM is a joint controller with each of the sites (MMUH, MUH, and SVUH) for processing of personal data. This is reflected in the joint data controllership agreements.

Each study site is an independent data controller.

There will be no sharing of personal data between sites.

Any data that is sent to either UCC or UHAM will be model parameters or the data will be considered anonymised in the hands of the third part, including binding terms not to attempt to identify individuals from the pseudonymised data.

Step 2
Upon receipt of the pseudonymised data from UCC, each site will independently analyse the data using a local instance of AI software (federated data analysis)

All analysis will take place locally in each site, on a local instance of the software. There is no cloud-based processing.

Step 4
MMUH and SVUH will share pseudonymised data with MUH.

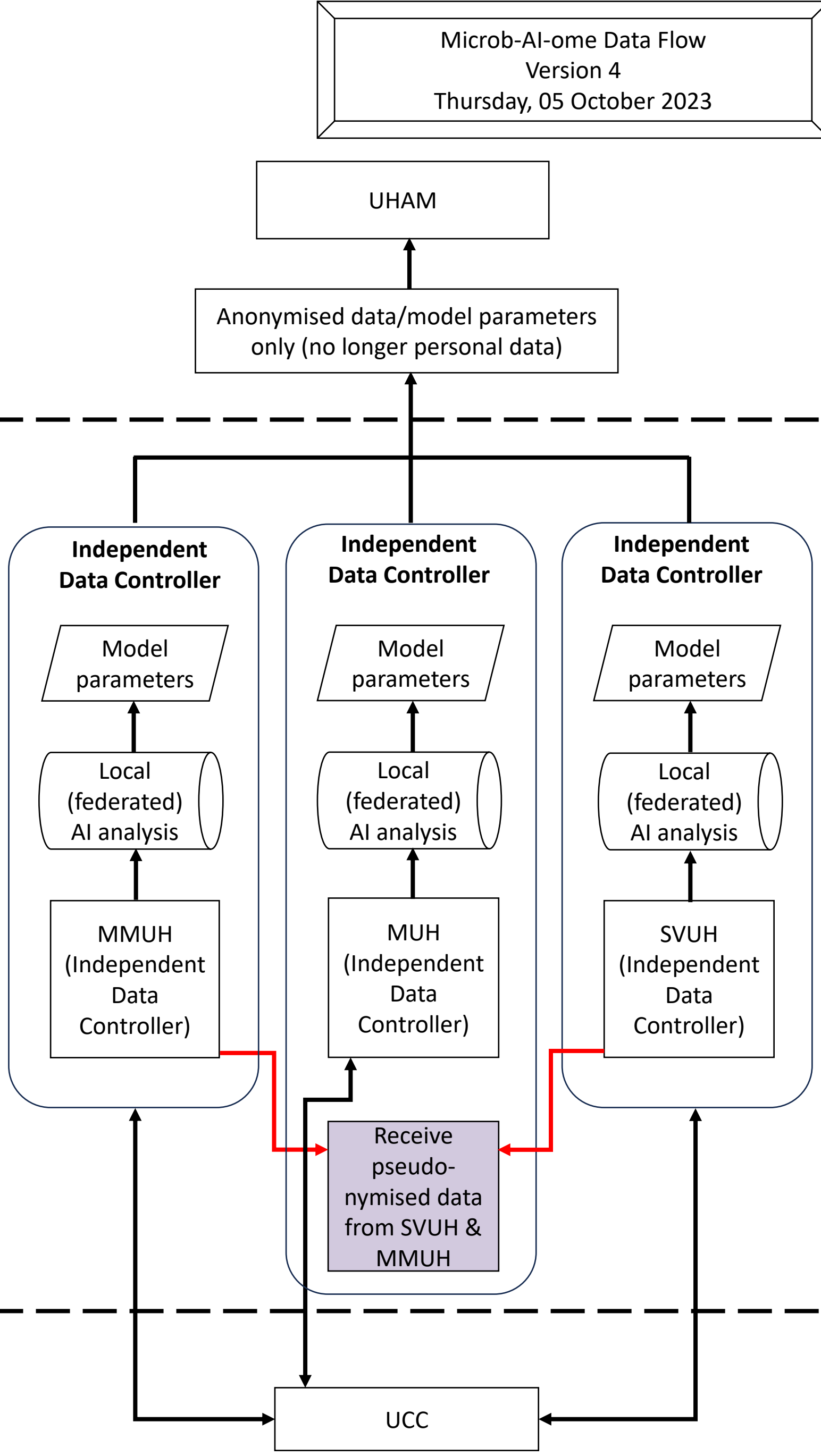
MUH will hold the pseudonymised clinical and processed microbiome data from UCC for each site.

MUH will act as an independent data controller.

Step 1
Stool samples will be sent with code to UCC for microbiome sequencing analysis.

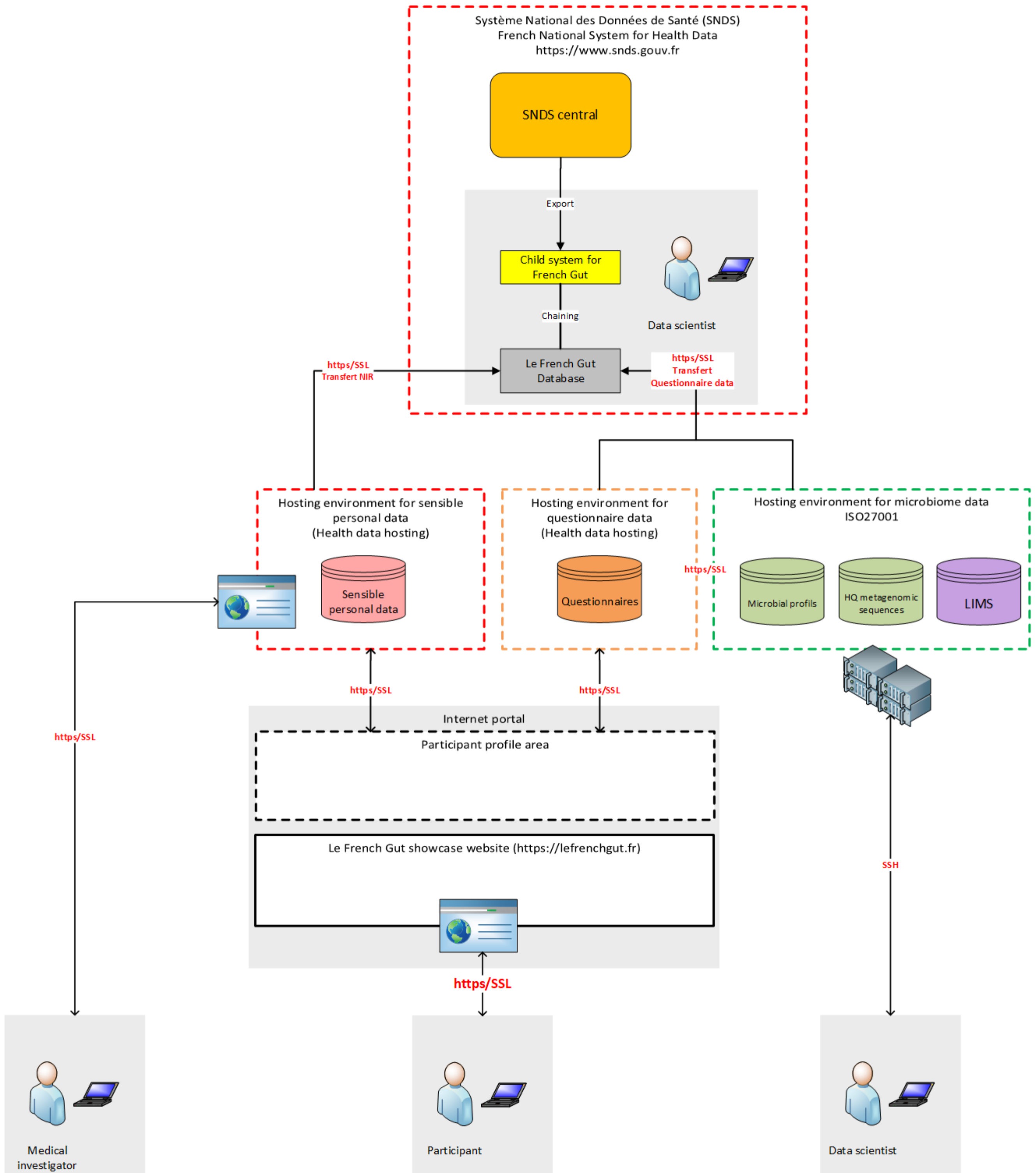
UCC will return the processed sequencing data to each site.

UCC will enter into a material transfer agreement which will include a clause to state that the pseudonymised data that is generated during microbiome sequencing shall be considered anonymised in the hands of UCC and UCC shall not attempt to identify the data subjects.



Acronyms:
 UHAM = Universität Hamburg
 UCC = University College Cork
 MMUH = Mater Misericordiae University Hospital
 MUH = Mercy University Hospital
 SVUH = St Vincent's University Hospital

Appendix 4 – Diagrammatic representation of data capture, processing, flow and governance (France).



Appendix 5 – Service level agreements within Ireland (incorporating data governance).

This Service Level Agreement (SLA) made the day of 2023

And made between:

- 1) Mater Misericordiae University Hospital (Company Registration Number 351402) having its registered office at Eccles Street, Dublin 7 (the “**MMUH**”) (the “**Coordinator**”); and
- 2) Mercy University Hospital (“**MUH**”) (“**the Clinical site**”) with registered address of Grenville Place, Cork City, Cork, Ireland.

Together known as the **Parties**. The Parties agree to enter into this SLA and agree to the following terms and conditions:

Background to this SLA:

- (A)** In conjunction with Bowel Screen Ireland, the Coordinator has been working and collaborating both at national and European level with the European Health and Digital Executive Agency and Universitaet Hamburg (UHAM) Germany to advance the Microb-AI-ome Project which project relates to the federated artificial intelligence for privacy preserving international stratification of colorectal cancer patients based upon Regulation (EU) No. 2021/695 of the European Parliament establishing Horizon Europe. (“**the Project**”).
- (B)** The Coordinator executed the Consortium Agreement dated X and the Grant Agreement Project 101079777 - Microb-AI-ome dated X, together known as the “**EU Agreements**” and entered into between Universitaet Hamburg (UHAM), UNIVERSITY COLLEGE CORK - NATIONAL UNIVERSITY OF IRELAND, CORK (UCC), GNOME DESIGN SRL (GND), TP21 GMBH (TP21), RESEARCH INSTITUTE AG & CO KG (RI), INSTITUT NATIONAL DE RECHERCHE POUR L'AGRICULTURE, L'ALIMENTATION ET L'ENVIRONNEMENT (INRAE), ASSISTANCE PUBLIQUE HOPITAUX DE PARIS (APHP), and MMUH. As beneficiaries both MMUH and UCC are funded for the Project in Ireland.
- (C)** As additional clinical sites are required in Ireland for the Project, MMUH has been funded to project manage the Irish clinical sites associated with this Project and to liaise with and report to UHAM on the Project and to fully comply with the EU Agreements. MMUH has notified UHAM that MUH is a designated clinical site in Ireland for the Project and that its eligible costs will be provided to MMUH for payment in accordance with the EU Agreements.
- (D)** The EU Agreements are attached at Appendix 1 of this SLA. The funding contribution to MMUH is for the advancement of the Project within the agreed clinical sites and coordinators in Ireland (the “**Network Members**”) which comprises MMUH, SVUH, Mercy University Hospital (MUH), UCC and Bowel Screen Ireland which funding is subject to the terms and conditions contained in the EU Agreements. MMUH is the lead for the Network Members in Ireland and MMUH together with UCC has accepted the EU Agreements on behalf of the Network Members. Any clinical trial activities shall be subject to a separate written clinical trial agreement between the relevant Network Members, Affiliated Hospitals and/or third parties.

The Parties to this SLA agree as follows:

In consideration of the mutual benefits to each of the Network Members by collaborating on the Project, MUH agrees the following:

1. The funding to MMUH is given under the terms and conditions contained in the EU Agreements. MUH hereby undertakes to MMUH to comply with all provisions of the EU Agreements (as if it were itself bound by the EU Agreements in a like manner to MMUH) and

to do all acts and things as may reasonably be required of it by MMUH in order to facilitate compliance by MMUH with the requirements of the EU Agreements insofar as they relate to MUH's participation in the Project. If there are any conflicts or inconsistencies between the provisions of this SLA and the EU Agreements, the EU Agreements will prevail.

2. Notwithstanding the date of execution, this SLA shall be deemed to have taken effect from the (INSERT) 2023, being the Effective Date, and shall continue in full force and effect until the 30 September 2026 being the End Date, unless terminated early in accordance with this SLA.
3. Insofar as it relates to MUH's participation in the Project, MUH accepts the following responsibilities:
 - (a) To carry out the tasks which it is specified to perform in connection the Project in a timely manner and in accordance with this SLA to ensure the efficient implementation of the Project. This includes but is not limited to:
 - (i) having in place appropriate data storage;
 - (ii) to ensure the secure transfer of bio-samples to UCC;
 - (iii) to securely transfer relevant data directly to MMUH and as required to the EU partners as required under the EU Agreements;
 - (iv) to assist and fully comply with any audit as described under the EU Agreements;
 - (v) to assist and cooperate with MMUH in meeting any reporting requirements in respect of the Project required under the EU Agreements. Specifically, MUH agrees to provide to MMUH all information and documents required to be submitted onto the Portal Participant Register as detailed in the EU Agreements;
 - (vi) maintaining a segregated set of accurate and proper accounts in respect of the Project and shall make such accounts available for audit or inspection in accordance with the EU Agreements, via MMUH, if required. The MUH shall cooperate fully with any inspections and or audits concerning the Project required by MMUH or under the EU Agreements;
 - (vii) to retain all relevant records for the Project as detailed in the EU Agreements and for the relevant period of time;
 - (viii) to recruit a Clinical Nurse manager WTE 0.5 for the duration of the Project.
 - (b) To notify promptly MMUH of any significant information, fact, problem or delay likely to affect the Project.
 - (c) To inform MMUH of relevant communication it receives from third parties in relation to the Project.
 - (d) To take reasonable measures to ensure the accuracy of any information or materials it supplies to MMUH and promptly correct any error therein of which it is notified.
 - (e) To furnish the necessary qualified Personnel for the implementation of the Project. Specifically, MUH agrees that the endoscopy service should be delivered by BowelScreen Clinical Advisory Group approved Consultant Gastroenterologists or Consultant Colorectal Surgeons, or suitably qualified advanced nurse practitioners registered with An Bord Altranais. However, MUH shall be solely responsible for the performance of the Project by its personnel, unless otherwise agreed in writing including via a Clinical Trial Agreement for a Clinical Trial.

4. Upon receipt by MMUH of sufficient funds for the Project under the EU Agreements and within a reasonable time, MMUH will disburse MUH eligible costs as described in the EU Agreements for relevant work completed on the Project within the Project timeline.
5. The terms for the ownership and management of intellectual property developed during Clinical Trials carried out under the Project will be defined in the respective Clinical Trial Agreements for the relevant Clinical Trial. However, MUH must give all parties to the EU Agreements access to background information which is any data, know-how or information, whatever its form or nature (tangible or intangible) including any rights such as intellectual property rights that is (a) held by the beneficiaries before they acceded to the EU Agreements and (b) needed to implement the action or exploit the results. If background information is subject to rights of a third party, the beneficiary concerned must ensure that it is able to comply with its obligations under the Agreement.
6. MUH agrees to use any information marked as confidential ("**Confidential Information**") by any Network Member solely for the purposes of the Project and agrees not to disclose any such Confidential Information to a third party unless (i) that information becomes public knowledge; (ii) the Confidential Information was already known by the receiving Research Partner as evidenced by written record; or (iii) required by law and/or any regulatory authority. This obligation shall remain for a period of 5 years from the End Date. The confidentiality obligations under this Agreement and the Grant Contract shall not prevent the communication of Confidential Information to MMUH.
7. The MUH and each Network Member will furnish each other with copies of proposed publications in respect of the Project or in respect of any foreground intellectual property including results and findings developed as part of the Project, 3 weeks in advance of the proposed submission for publication. The Network Members, acting reasonably, shall have a period of three weeks to: (i) require a delay of the publication for up to 3 months for the purposes of filing a patent application; (ii) require the removal of any proprietary or Confidential information; or (iii) recommend changes which the publishing Network member shall make at its discretion. Permission is presumed if no written objection is received within the 3 week period. The Network Members acknowledge that any publication and/ or dissemination relating to a Clinical Trial shall be governed by the respective Clinical Trial Agreement.
8. Liability:
 - i. MUH undertakes its part of the Project at its own risk.
 - ii. No Network Member is responsible to any other Network Member for any claims in respect of indirect, consequential or incidental loss or damages, including any claims by a third party against another Network Member.
 - iii. Each Network Member shall be liable to MMUH for any losses or damages suffered by MMUH as a consequence of that Network Member's failure to perform the obligations required of MMUH under the EU Agreements. In the event that it is not possible to attribute the default to any Network Member, the amount claimed under the EU Agreements shall be apportioned between all of the Network Members pro-rata to the amount of funding allocated to each Network Member.
 - iv. MUH performs its obligations under this SLA as an independent entity and accordingly, the responsibility of complying with all legal requirements (including payment of tax) falls upon MUH and is to be discharged wholly and exclusively by MUH.

- v. Subject to clause 8(iii) and 8(vi) where no cap on liability shall apply, the maximum liability of a Network Member under this SLA shall not exceed the sum to be transferred under this SLA.
- vi. Nothing in this SLA limits or excludes MUH's liability for (a) death or personal injury resulting from negligence; or (b) any fraud or for any sort of liability which, by law, cannot be limited or excluded.

MUH acknowledges that any and all liability relating to a Clinical Trial shall be governed by the respective Clinical Trial Agreement.

9. MUH shall maintain adequate levels of insurance for the duration of the Project. The responsibility for the clinical trial insurance for each Clinical Trial shall rest with MUH.
10. For the purpose only of fulfilling its reporting obligations under the EU Agreements, MUH agrees to provide MMUH promptly on request (and where it is legally able to do so) any information relating its participation in the Project.
11. On termination of the EU Agreements, this SLA will terminate immediately.
12. Where MUH fails to comply in any material respect with any obligation, and either (i) such failure is not susceptible to remedy, or (ii) is not remedied to the satisfaction of UHAM, acting reasonably, within 30 calendar days, MMUH may terminate this SLA. Payments due shall be made pro rata, up to the date of termination.
13. In the event of the termination of MUH to this SLA, any portion of the funds already allocated to MUH that has not been expended in connection with the Project and is not irreversibly committed shall be returned to MMUH. Any and all costs that MMUH incur under the EU Agreements as a result of MUH termination must be discharged in full by MUH. All committed costs will be honoured in the event of termination of this SLA. The provisions relating to confidentiality, indemnity, liability, settlement of disputes and clause 21 of this SLA shall survive the expiration or termination of this SLA.
14. MUH and MMUH will (and shall procure that its personnel shall) do all such acts and things as is required to comply with all applicable Data Protection legislation as applicable in Ireland and as defined in the EU Agreements, regulations, codes of practice relating to the protection, processing of personal data or privacy or any amendment and re-enactments thereof. It is not anticipated that any personal data will be transferred under this SLA, any such transfer shall require an appropriate data protection agreement to be executed prior to transfer. The Parties agree that any pseudonymised data provided under this SLA shall be considered anonymous data in the hands of the data recipient, on the condition that the recipient does not have access to the pseudonymisation code or any other means to re-identify the data subjects and the data recipient agrees not to attempt to re-identify data subjects using any means available. The recipient shall take all necessary measures to ensure that the pseudonymised data remains anonymous and shall not attempt to re-identify the data subjects or disclose any information that may enable such re-identification. The recipient shall promptly notify the data provider if it becomes aware of any attempt or unauthorised access to the pseudonymised data that may compromise the anonymity of the data subjects. Please see Appendix 2 of this SLA for the data flowchart.
15. MUH and MMUH shall comply with their obligations under all applicable Export Control Laws being any United Nations or EU trade sanctions, restrictive measures, EU law and Applicable

Law that apply in Ireland from time to time, which impose arms embargoes or control the export of goods, technology or software, including weapons of mass destruction and arms, military and security equipment and dual-use items (items designed for civil use but which can be used for military purposes). It is not anticipated that any restricted materials be transferred under this SLA, any proposed transfer shall require prior notification and agreement by the transferee.

16. With regard to the EU Agreements and grant funded activities and underlying research activities it is agreed as follows:

16.1 MUH will ensure that all grant funded activities and underlying research activities funded by the EU Agreements, are (i) organised and undertaken within a framework of best practice and (ii) conducted in accordance with the highest standards of scientific integrity and research methodologies. MUH will ensure that it has appropriate policies and procedures and reliable systems in place, in relation to research governance and prevention and investigation of misconduct, in place to demonstrate and verify compliance, as required, from time to time by MMUH. The MUH shall furnish in writing to MMUH full details of any proven misconduct directly relating to the Project.

16.2 MUH acknowledges and agrees that, as per the EU Agreements, MUH will be wholly responsible for the conduct of individual underlying research activities. Having regard to the EU Agreements:

- a. In the event of the sponsor being MUH, MUH hereby confirms to MMUH that it shall ensure that the appropriate contractual arrangements/clinical trial agreements are in place prior to the commencement of the clinical trial activity; and
- b. In the case of underlying research activities where a sponsor is another Network Member or an external third party, i.e. not a Network Member, MUH shall notify the sponsor by letter that the sponsor shall be wholly responsible for the conduct of the clinical activity and clarifies the sponsor's role in the clinical activity.

16.3 Each research partner shall be solely liable for obtaining necessary approvals in respect of:

- (a) any grant funded activities for which it is responsible; and/or
- (b) underlying research activities facilitated by it. Upon request from MMUH, MUH shall furnish an Approvals Declaration (together with copies of any relevant Approval(s)) to MMUH without undue delay.

17. The following documents shall be construed as mutually explanatory of one another. In the event of any inconsistency between the documents, interpretation shall be made by referring to these documents in the following order of precedence:

- (a) The Consortium Agreement;
- (b) Grant Contract; and
- (c) this SLA.

18. The organisation and operational requirements for governance are outlined in the EU Agreements. MUH agrees to do all acts and things (to the extent not already done) necessary

for the establishment of the committees, offices and other organisational structures and procedures in respect of the Project.

19. The signature of MUH by means of a scan or digitization of the original signature (e.g. a scan in PDF format) or an electronic signature (e.g. via DocuSign), counts as an original signature with the same validity, enforceability and permissibility.
20. This agreement shall be governed by Irish law and subject to the exclusive jurisdiction of the Irish courts.

As evidence of agreement to the above terms, please have an authorised signatory signed where indicated below.

For MMUH

Signed: _____

Print Name: _____

Authorised Signatory of Mater Misericordiae University Hospital

For Mercy University Hospital

Signed: _____

Print name: _____

Authorised Signatory of Mercy University Hospital

Dated:

APPENDIX 1 – EU Agreements

APPENDIX 2 – DATA FLOWCHART

Step 3
 Each site will independently send aggregate data to UHAM.
 UHAM will not have access to any personal data.
 UHAM is a Joint Controller with each of the sites for the processing of personal data. This will be reflected in the Study Collaboration Agreement

Each study site is an independent data controller.
 There will be no sharing of personal data between sites.
 Any data that is sent to either UCC of Hamburg will be aggregated data or the data will be considered anonymised in the hands of the third party, including binding terms not to attempt to identify individuals from the pseudonymised data.

Step 2
 On receipt of the pseudonymised data from UCC, each site will independently analyse the data using a local instance of the AI software.
 All analysis will take place locally in each site, on a local instance of the software. There is no cloud based processing.

Step 4
 The Mater Hospital & St Vincent's University Hospital will share pseudonymised data with the Mercy Hospital.
 The Mercy hospital will hold the pseudonymised clinical and analysed microbiome data from UCC for each site.
 Mercy hospital will act as an Independent Data Controller.

Step 1
 Stool Sample will be sent with code to UCC for analysis.
 UCC will return the analysed data to each site.
 UCC will enter into a Material Transfer Agreement which will include a clause to state that the pseudonymised data that is generated following analysis shall be considered anonymised in the hands of UCC and UCC shall not attempt to identify the data subjects.

