COLLABORATION AGREEMENT

by and between

The National Institute for Health and Welfare THL
POB 30
FI-00271 Helsinki
Finland

- hereinafter referred to as „**THL**" -

and

Bayer AG
Müllerstraße 178
13352 Berlin
Germany

- hereinafter referred to as „**Bayer**" -

- Bayer and THL are sometimes referred herein, individually, as a **"Party"** and collectively, as the **"Parties"** -

Preamble

WHEREAS, the Parties are interested in the conduct of a research project, entitled "Gastrointestinal Bleedings in the general population of Finland – Occurrence and risk factors" (hereinafter referred to as **"Research Project")** and described in more detail in the approved application for data attached hereto as **Appendix 1**, that is part of a PhD thesis by Pareen Vora, an employee of Bayer (hereinafter referred to as the "**Researcher**").

WHEREAS, THL possess resources and data necessary for the conduct of the Research Project, in particular access to the data of participants of the FINRISK surveys as described in Appendix 1 (hereinafter referred to as the "**FINRISK Data**").

THEREFORE, the Parties hereto agree as follows (hereinafter referred to as the **"Collaboration Agreement"**):

§ 1 - Subject Matter of the Collaboration Agreement

The subject of the Collaboration Agreement is the conduction of the Research Project.

§ 2 - Performance of the Research Project

2.1 The Research Project shall be conducted by a joint research group. The research group shall be made up of the Researcher, appointed as data-analyst, and several advisors/collaborators.

THL hereby nominates as its advisors/collaborators:

Markus Perola,
Veikko Salomaa,
Markku Peltonen,

Bayer hereby nominates as its advisors/collaborators:

Gunnar Brobert

2.2 THL shall prepare FINRISK Data sets for the Research Project, as far as necessary and agreed between Parties. THL shall provide access to the FINRISK Data to the Researcher for the duration of the Research Project. In this regard the Researcher will be given the status of a visiting researcher at the THL and THL shall provide him with the resources which THL considers to be necessary.

2.3 The Researcher shall use the FINRISK Data only for the purposes of this Collaboration Agreement.

2.4 The Researcher should access the provided FINRISK Data using a network drive set up by THL and should do the data analysis on the individual level data for the Research Project in Finland with a computer provided by THL. Secure data access (such as passwords, firewalls, etc.) shall be in place to ensure that the data are kept secure.

2.5 The Researcher and the advisors/collaborators shall collaborate for an optimal interpretation of the FINRISK Data.

§ 3 - Term and Timelines

3.1. This Collaboration Agreement is effective upon last signature of the Parties hereunder and ends upon the completion of the Research Project.

3.2. At the Researcher's request THL may extend the term and timelines of the Research Project by a new decision promptly sent to the Researcher. THL agrees that such request for extension will not be unreasonably refused.

3.3 Each Party will have the right to terminate this Collaboration Agreement forthwith by 6 months prior written notice to the other Party.

3.4 Each Party will have the right to terminate this Collaboration Agreement forthwith by a written notice to the other Party with immediate effect if:
- the other Party commits a material breach of this Collaboration Agreement and fails to remedy the same within 30 days after receipt of a written notice giving particulars of the breach and requiring it to be remedied;
- Researcher ceases to be employed (or otherwise engaged by) Bayer;
- Party ceases, is likely to cease, or threatens to cease carrying on business or is being acquired by a third party.
- national or EU privacy or other authority forbids or limits a Party's right to use and/or transfer the FINRISK Data
- if THL reasonably determines that such processing of FINRISK Data would not be or is likely not to be in accordance with the data protection regulation currently in force

3.5 The right to terminate this Collaboration Agreement given by this clause 3 will be without prejudice to any other right or remedy of either Party in respect of the breach concerned, if any, or any other breach..

3.6 All provision of this Collaboration Agreement which by nature should survive termination of this Collaboration Agreement shall so survive such termination. This shall include without limitation provisions relating to rights to results, confidentiality and publications.

§ 4 - Rights to Results

4.1 The rights to all results that are generated or otherwise made in connection with the performance of the Research Project (hereinafter referred to as "Results") shall be jointly owned by THL and Bayer.

4.2 For the avoidance of doubt, the FINRISK Data themselves are in no case considered as Results.

§ 5 - Confidentiality

5.1. All information, data and material exchanged by the Parties in connection with the Research Project which has been explicitly marked or otherwise identified as “confidential” or “secret” at the time of the disclosure(“Confidential Information”) shall be treated by the receiving party as confidential.

5.2. The receiving Party shall for a period of 5 years after the end of the Research Project i) hold the Confidential Information in confidence and not disclose it to any third party, without the other Party’s prior written consent, ii) only use the Confidential Information for the purposes of this Collaboration Agreement, and iii) take any reasonable steps to the effect that each person employed at the receiving party to whom disclosure of the Confidential Information is made will not be made under less stringent confidentiality obligations as applies for the receiving Party under this Collaboration Agreement.

5.3. Such obligations of confidentiality and non-use shall not apply to any Confidential Information which the receiving Party owns or for which the receiving Party can show i) is already lawfully known to the receiving Party at the date it was disclosed to it by the other Party and is or becomes free of restriction on the disclosure or use in question, or ii) is or becomes generally known or freely available to the public (except by reason of any breach by the receiving Party of its obligations hereunder), or iii) is disclosed to the receiving Party free of restriction on the disclosure or use in question, by a third party who was entitled to make such unrestricted disclosure, or iv) is independently developed by the receiving Party, or v) is disclosed, retained or maintained to comply with law or an enforceable judicial order.

5.4. For avoidance of doubt it is stated that personal data shall be always be treated as Confidential Information even if not marked as confidential or secret. The term of confidentiality with regard to personal data is not limited to the 5 year period defined above in clause 5.2.

§ 6 - Publication

6.1 Results shall be published in a joint publication with THL and Bayer.

6.2 In case of a Party's sole publication, this Party shall give appropriate acknowledgement in the publication to the scientific input of the other Party’s employees and give reasonable consideration to any request of the other Party to revise the publication or remove any Confidential Information of the other Party from the publication.

§ 7 - Compliance

7.1 THL acknowledges that this Agreement is not conditioned on any pre-existing or future business relationship between Bayer and THL. It is also not conditioned on any business or other decisions THL has made or may make relating to Bayer or Bayer products.

7.2 Both Parties represent and warrant that any personal data have been and will be collected, stored, structured, transferred, analyzed or in any other way processed by the respective Party only in strict compliance with all applicable data protection legislation.

§ 8 - Payment

8.1 THL will charge Bayer for costs of preparing the FINRISK Data sets for the Research Project as determined in **Appendix 3**.

8.2 Any payments hereunder will be made by Bayer upon receipt of an invoice (to be issued in the name and on the letterhead of THL) which meets all requirements according to applicable legal Value Added Tax ("VAT") rules.

8.3 Any invoices shall be sent to: Bayer AG, Rechnungseingangsstelle, 51368 Leverkusen, and will bear a reference to Montse Soriano-Gabarró, Epidemiology, cost center GV78910000, PSP-element LPHGV-RV-M-212999_RIV_MP, and a purchase order number which will be announced to THL in writing, BAYER will inform THL immediately regarding any change to this arrangement.

§ 9 - Miscellaneous

9.1 If any of the provisions of this Collaboration Agreement will be held to be invalid or unenforceable, the validity or enforceability of the remaining provisions of this Collaboration Agreement shall not in any way be affected or impaired thereby. The Parties will promptly agree upon replacement provision(s) which approximate as closely as possible the spirit and intent of the invalid provision(s).

9.2 FINRISK Data is provided “as is” without any warranties or guarantees, in particular with respect to the fitness for a specific purpose, or that the use of the FINRISK Data will not infringe any intellectual property rights of third parties.

9.3 THL’s liability towards Bayer shall be limited to the payments made by Bayer under this Collaboration Agreement, except for cases of gross negligence or willful misconduct, or any damages which result from injury to life, limp or health.

9.4 The failure of either Party to enforce or require performance of any of the provisions of this Collaboration Agreement, or to exercise any right herein provided, shall in no way be construed as a waiver of such provision or right or thereafter affect such party’s right to enforce any provision of this Collaboration Agreement.

9.5 Amendments and extensions to this Collaboration Agreement shall not be effective unless in written form and signed by both Parties.

9.6 The interpretation of this Collaboration Agreement and the resolving of any disputes will be governed by the laws of Finland in force at the time. Any disputes that cannot be resolved between the Parties will be taken to the district court of Helsinki for resolution.

Authorized signature of THL

Date	
Signature	
Name	Pekka Jousilahti
Title	Research Professor, Director of the FINRISK Study

Authorized signature of THL

Date	6.8.2018
Signature	
Name	Anne Juolevi
Title	Data Manager

Authorized signature of Bayer

Date	2.7.18
Signature	ppa.
Name	Dr. Stefan Schröder
Title	Head Data Generation & Business Excellence

Authorized signature of Bayer

Date	29.6.18
Signature	i.v.
Name	Montse Soriano-Gabarró, MD, MSc
Title	Head Epidemiology

Acknowledgment of Researcher

Date	29.6.18
Signature	
Name	Pareen Vora
Title	M.Sc., Epidemiologist

Appendices:

Appendix 1. Approved application for data
Appendix 2. THL's Instructions for safety and information security
Appendix 3. Budget and invoicing schedule

Appendix 1. Approved application for data

21-12-2017

Application FR2017_34

Gastrointestinal Bleedings

Approved

21-12-2017

Application Form

Research project full title

Gastrointestinal Bleedings in the general population of Finland – Occurrence and risk factors

This is an amendement of previous approved application

no

If yes, what is/are the previous project permit code/s?

Research project start date

Mon Jul 31 00:00:00 GMT 2017

Research project end date

Tue Dec 31 00:00:00 GMT 2019

Research project plan (describe in detail the aims of the study and analysis plan)

This project is part of a PhD thesis by Pareen Vora. The project will be based on data form Finland. The data to be used comprises of the National FINRISK surveys and linked to the National Health Registers (Hospital discharge register, Death Register, cancer register (if required) and Drug reimbursement register).

The research objective of this project is to investigate the occurrence and risk factors of gastrointestinal (GI) bleedings in the general population of Finland.

The FINRISK cohorts comprise the respondents of representative, cross-sectional surveys that were carried out every 5 years since 1972, to assess the risk factors of chronic diseases (e.g. CVD, diabetes, obesity, cancer) and health behavior in the working age population, in 3-5 large study areas of Finland. Background information such as socioeconomic status, chronic diseases, medical history, diet, exercise, anthropometric measures, smoking and alcohol was collected by questionnaires and during a clinical visit. The cohort sizes are 6000-8800 per survey.

The patients from the FINRISK study have been linked to the national health registers using personal identification number (PIN). Finland introduced a PIN system in 1964, and since then practically all administrative registers have

included this unique identification code. The follow-up of these patients has been conducted from the enrollment to the FINRISK surveys up to the onset of a GI bleed, death, emigration, or end of follow-up by linking to the national health registers.

The outcome events will be identified from the National Hospital Discharge Register and from the National Causes-of-Death Register using following ICD-codes:

ICD-10: I850, K226, K250, K252, K254, K256, K260, K262, K264, K266, K270, K272, K274, K276, K280, K282, K284, K286, K290, K5280, K625, K661, K920, K921, K922.

ICD-9: 4560A, 5307A, 531*B, 532*B, 5621C, 5780A, 5781A, 5781B

ICD-8: 53190, 53192, 53290, 53390, 53501, 53507, 78450, 78570

The PhD research will focus on the occurrence of GI bleeding in the general population by socio-demographic variables, regional differences and secular trends. Also, we plan to test hypotheses about potential risk factors for gastrointestinal bleeding including both upper and lower GI bleeds. Potential factors to be considered are demography (e.g. age, sex), lifestyle factors (e.g. BMI, smoking, alcohol use), medications (e.g. NSAIDs and anticoagulants), co-morbidities (e.g. GI diseases), family history of chronic diseases (if available).

The project is divided in to several stages.

•Literature review

•Relevant approvals in order to initiate the project

•Drafting and finalizing protocol

•Data description and verification in order to understand the data.

•Programming and analysis of the data.

•Drafting and finalizing study reports

•Drafting manuscripts and abstracts for conferences.

Short summary in plain language (in Finnish, if possible) to be published on THL Biobank's webpages

Suolistoverenvuodot ovat tavallinen ja usein vakava kliininen ongelma. Niitä esiintyy eri syistä, mutta usein altistavana tekijänä on lääkehoito, kuten erilaiset särkylääkkeet ja varsinkin verenohennuslääkkeet. Tässä projektissa tutkitaan suolistoverenvuotojen epidemiologiaa ja niille altistavia tekijöitä. Tietoa voidaan käyttää suolistoverenvuotojen ehkäisyyn ja entistä turvallisemman lääkehoidon suunnitteluun.

Date when short summary can be published

Mon May 08 00:00:00 GMT 2017

Place of research, including place of sample and/or data analysis

1. THL-National Institute for Health and Welfare, Helsinki, Finland (Data Analysis would be conducted in Finland)
2. Bayer AG, Pharmaceuticals, Berlin, Germany
3. Ludwig-Maximilians-University, Munich, Germany (PhD enrollment)

21-12-2017

Description of the research group and the role of each group member

This project is part of a PhD thesis by Pareen Vora enrolled at Ludwig Maximilians University (LMU), Munich Germany. Pareen Vora is an epidemiologist employeed at Bayer AG, Global Epidemiology. This Project is in collaboration with Veikko Salomaa and Markus Perola from THL and the work on the data would be conducted in Finalnd. Also, other FINRISK investigators are also welcome to contribute to the project.

Role:-
Pareen Vora, Bayer and LMU: Research Student
Gunnar Brobert, Bayer: Thesis Supervisor
Georg Hasford, LMU: PhD Advisor
Veikko Salomaa, THL: Project Supervisor, Advisor and Collaborator
Markus Perola, THL: Project Supervisor, Advisor and Collaborator

Specific selection criteria of study participants (if applicable)

All individuals taking part in the FINRISK surveys from 1972 to 2012 will be included.

Requested data (information on variables is found at https://kite.fimm.fi)

•Sociodemographic variables (e.g. age, sex, study area, survey-year, socioeconomic status)
•Clinical measurements (e.g. BMI, waist/hip-ratio, blood pressure)
•Lifestyle variables (e.g. BMI, smoking, alcohol consumption, coffee drinking)
•Laboratory variables (e.g. lipids, crea, gluc, gamma glutamyl transferase, other liver function tests if they exist, hsCRP)
•Medications (e.g. NSAIDs and ASA to the extent data exist, anticoagulants, antihypertensive medications, hypoglycemic medications)
•Comorbidities (e.g. GI-diseases, cardiovascular diseases, diabetes)
•Outcome events, as described above.

What national register data is requested (if applicable) ? Explain why access to each registry is required.

•Causes of Death Register
•Hospital Discharge Register
•Cancer Register
•Drug Reimbursement Register

What study results will be returned to THL Biobank (if any)?

Study results from the analysis of the data.

21-12-2017

Expected date of data return

Are biological samples requested ?

no

Type and amount of biological samples requested

Sample analysis contact person (name, institute and e-mail address)

Principal Investigator's short evaluation of the ethical aspects of the project

This project is within the limits of ethical approvals of the Biobank and informed consents of FINRISK

Project related keywords (max 5 keywords)

Gastrointestinal hemorrhages, anticoagulants, non-steroidal anti-inflammatory analgesics, acetylsalicylic acid

Planned publications

1.Risk factors associated with the gastrointestinal bleedings in the Finnish population

2.The descriptive epidemiology of gastrointestinal bleedings in Finland.

These will be published as original papers in international, peer reviewed scientific journals.

Funding information

Bayer AG will cover the salary of the data-analyst and the primary author of the papers as well as the costs of

preparing the data set for the project.

Invoice address (Service prices: www.thl.fi/biobank/researchers)

THL Biobank's registered area/s of operation to which the research project complies (please select) :

Promoting the population's health
Yes

Identifying factors involved in disease mechanisms
Yes

Disease prevention
Yes

Developing products that promote the welfare and health of the population
No

Developing products and treatments for diseases
No

Other
No

Targeted Resources

Applied items
Catalog item
FINRISK 1972-1987 (samples depleted)
FINRISK 2012
FINRISK 2007
FINRISK 2002
FINRISK 1997
FINRISK 1992
Catalog item

Members of the Application

Main applicant			
Screen name	First name	Last name	Email
pareen.vora	Pareen	Vora	pareen.vora@bayer.com
Screen name	First name	Last name	Email

Application members			
Screen name	First name	Last name	Email
veikko.salomaa	Veikko	Salomaa	veikko.salomaa@thl.fi
markus.perola	Perola	Perola	markus.perola@thl.fi
Screen name	First name	Last name	Email

Application members
Email
gunnar.brobert@bayer.com
Email

History		
Actor	Description	Timestamp
marketta.taimi	Approval comments: Pyydän FINRISKI-johtaja Pekka Jousilahtea hyväksymään Pareen Voran hakemuksen Gastrointestinal Bleedings in the general population of Finland – Occurrence and risk factors, joka on saanut myönteiset arviot. Ryhmään ehdotetaan Markku Peltosta. terv. Marketta Taimi	2017-08-22 09:53:39.0
pekka.jousilahti	Approval comments: Ok. Pekka	2017-08-22 10:53:57.0
	Application approved	2017-08-22 10:53:58.0
Actor	Description	Timestamp

Appendix 2. THL's Instructions for safety and information security

Safety and information security

1. Access to premises and systems

1.1. The premises of the recipient must be secured through locking and other essential procedures to block unauthorized access to the premises and to the information stored there.

1.2. The recipient makes sure that the systems and devices where the material is being stored and handled are accessed only by persons with right to access the material.

1.3. Access to the material, which is stored in the systems or the devices, must be secured with licenses/access rights. The access rights and the rationale for the admittance must be verifiable and they need regular monitoring. Collective access rights are forbidden (i.e. the user names and passwords are personal and it is forbidden to transfer them to another party), except for laboratory devices in which only basic information on samples is stored.

2. The software updating and and the prevention of malware

2.1. The recipient or a service provider authorized by the recipient must make sure that all the computers in the recipients network environment have updated antispyware software in use.

2.2. The recipient or a service provider authorized by the recipient will take care of the updates for the devices, systems and software, especially the information security updates.

3. The storage and transfer of the material

3.1. The devices and other storage devices used to handle or store the material must be in a locked space, when they are not under supervision to prevent unauthorised usage and theft.

3.2. The material must be stored in a way, that doesn't compromise the data privacy. The material including personal information must be stored encrypted or otherwise protected with access control regardless of whether the information is identifiable or unidentifiable. Identifiable personal information must always be stored highly encrypted.

3.3. It is forbidden to store or transfer the material on public cloud computing services (i.e. Google Drive, Dropbox, etc.) if the servers are or might be located outside of European Union borders or if it is not possible to ensure the security of the server unless otherwise ordained. The same rules apply to the domicile of the cloud computing service provider.

3.4. It is forbidden to transfer the material through a public network (internet) without encryption (i.e. via e-mail without an encryption).

3.5. If the material is handled with a laptop or a transferrable media, it is required that the hard drive, media or the directory where the information is stored must be highly encrypted. The encryption must be activated when the computer or media is outside the premises. The use of transferrable media should be avoided where possible.

3.6. The Material should be stored and handled using network drive or any other centralized storage systems set up by the recipient institute, and not handled or stored on personal computers.

4. The maintenance and removal of the memory and other devices

4.1. When the device is removed from use, the hard drive where the material has

been stored or which has been used to handling the material must be overwritten or destroyed safely so the data privacy will not be compromised. This means overwriting the information at least three times or data shredding. All the mass storages must be removed and destroyed without compromising the privacy.

4.2. The transferrable drives (USB-drives, external hard drives, CDs, DVDs etc.) where material has been stored or if they have been used to handle the information, must be destroyed appropriately, for example by crushing or shredding, so the the privacy won't be compromised.

4.3. If the recipient uses an external service provider for the maintenance of the devices, other technical equipment or systems the recipient is responsible for signing a security contract with the service provider in written form. Before delivering the device or the other technical equipment for the maintenance the recipient must make sure that all the memory devices are removed, or the information is removed in another secure way, or the material is protected to minimize the risk of data disclosure.

4.4. In situations where the maintenance procedure via remote access is possible, the recipient must verify the identity of the service provider's maintenance person providing the procedures and make sure the recognition and log in mechanisms and the connections are secure.

5. Handling of material on the devices and in the environments of THL

5.1. If the handling of the material is done on the devices or in the environments provided by THL, THL will make sure that both the devices and the environments are according to the data safety requirements.

Appendix 3. Budget and invoicing schedule

Name of External Supplier/ External Partner (ES/EP): THL-National Institute for Health and Welfare	
	GIBSON_THL_Cost proposal, 27 November 2017
Project title	*Gastrointestinal Bleedings in the general population of Finland – Occurrence and risk factors GIBSON*
Description	*The objective of this project is to investigate the occurrence and risk factors of GIBs in the general population of Finland.*
Estimated date of delivery	*Q4 - 2019*
Currency	*_**X**_ €, __ GBP, __ US $, __ SEK*

Summary of costs	**Totals**
E.g. Tasks	0,00
Hours	56.064,00
E.g. Pass-through costs (if applicable)	0,00
E.g. Third party costs (if applicable)	0,00
TOTAL	**56.064,00**

(ES/EP) rates for Bayer		See examples below, as a reference only.
Level 1	0,00	E.g. Director/MD/PhD
Level 2	219,00	E.g. Epidemiologist
Level 3	219,00	E.g. Statistician
Level 4	0,00	E.g. Medical Writer
Level 5	0,00	E.g. Project Manager
Level 6	0,00	E.g. Administration

Item	**Quantity**	**Hours**	**Hourly Rate**	**Total Cost**	**Comments** *See examples below, as a reference only.*
Epidemiologist	1	128	219,00	28.032,00	Epidemiologist/Data Manager Salary: Basic rate 80 euros, plus 57% indirect employee costs plus 74% overhead share
Statistician	1	128	219,00	28.032,00	Post-doc statistician Salary: Basic rate 80 euros, plus 57% indirect employee costs plus 74% overhead share
				56.064,00	

Item	**Quantity**	**Units**	**Unit Cost**	**Total Cost**	**Comments**
Pass-through costs					
Data Fees	1	5	130,00	650,00	5 hours, a 130,00 €, total 650,00 € for building the data set.