Neuro-immune mechanisms of disease in Gastro-Esophageal Reflux Disease, and implications for treatment.

A Data Management Plan created using DMPonline.be

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Project abstract:

Gastro-esophageal reflux disease (GERD) is a chronic disorder with a significant impact on quality of life. GERD covers a wide spectrum of disease, from mild and intermittent symptoms to severe erosive esophagitis. Despite treatment with double dose PPI, up to 40% of the GERD patients fail to achieve complete symptom relief, and optimal treatment options for these patients are lacking. Even though a series of recent studies has provided more insight into the pathophysiology and symptom generation in GERD, the exact interplay between different compounds of the refluxate and the epithelium, afferent nerves, inflammatory pathways and symptom generation in different GERD subgroups remains to be elucidated. The first objective of this PhD project is to obtain more insight in the neuro-immune mechanisms underlying inflammation and symptom generation in different GERD subgroups. Esophageal biopsies will be analyzed, and we will correlate our findings to esophageal sensitivity in patients and healthy volunteers, before and after lidocaine infusion. The second objective is to examine novel treatment options in refractory GERD (rGERD). Citalopram will be used as neuromodulator in rGERD patients with reflux parameters within the physiological range. Effectiveness of radiofrequency energy delivery to the lower esophageal sphincter (Stretta®) will be evaluated in sleeve gastrectomy patients with postoperative GERD.

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Application DMP

Questionnaire

Describe the datatypes (surveys, sequences, manuscripts, objects …) the research will collect and/or generate and /or (re)use. (use up to 700 characters)

- Questionnaires

Symptom questionnaires will be filled in by patients at different time points, and by healthy volunteers at 1 time point. These questionnaires will be provided online, through qualtrics, available and endorsed by KU Leuven. After downloading the questionnaires in excel, data will be pseudonymized and the study code will be preserved in a separate file on the KU Leuven one drive, only accessible by the investigators involved in the project.

- Medical history

We will be working with medical history data of our patients/healthy volunteers. As this project concerns gastro-esophageal reflux disease patients, it is relevant to know their additional medical history, the nature and intensity of their complaints, their chronic and intermittent medication usage, history of surgery, demographics (height, weight, age). As healthy volunteers serve as controls, we will also have to make sure they are not taking any medication that could influence the study results, and do not have a history of gastrointestinal disorders. These data are kept in the patients files in KWS, and pseudonimized data (with study codes) will be kept at KU Leuven one drive, in a protected folder only accessible by the investigators.

- Endoscopy

Endoscopies will be performed in patients and healthy volunteers, to assess endoscopic features of gastro-esophageal reflux disease. Additionally, biopsies will be taken for evaluation in the lab (see below). Endoscopy reports will be uploaded in the patient files (kws), and will be accessible by the treating physician. The result of the endoscopy will be used in our data file on KU Leuven one drive, which will be pseudonimized, and the study code will be used for all analyses. The patient data and codes will be kept on a seperate file on KU Leuven one drive, and will only be accessible by the investigators.

- Multimodal esophageal stimulation

In patients and healthy controls, we will perform esophageal sensitivity testing using a specially designed probe (Mui Scientific, Canada). The probe will be inserted in the lower esophagus through the nose or mouth, and esophageal stimulation will be given with balloon distension (balloon filling with saline up to 60mL), and acid perfusion (pH of 1) in the distal esophagus. The results of the stimulation will be noted in a paper CRF, and later uploaded in a file using the study code on KU Leuven one drive, only accessible by the investigators.

- Biopsy collection

Esophageal and duodenal biopsies will be collected in patients and healthy volunteers. Part of the biopsies (2 duodenal, and 4 esophageal) will be sent to the pathology department at UZ Leuven, for histology and immunohistochemistry. 4 esophageal biopsies will be collected and frozen in OCT, and kept until analysis (immunohistochemistry). 2 biopsies will be used for protein analysis, and 2 for RNA analysis. In some of the patients, 4 esophageal biopsies will be mounted in ussing chambers, to assess esophageal permeability measures (see below). All of the biopsies will be kept with the study code of the patients, and the results of the ones going to the UZ Leuven pathology department will be uploaded in the patient files accessible by treating physicians (KWS).
In a previous study performed by a colleague investigator, esophageal biopsies were captured between 2020 and 2021 from 42 patients with occasional heartburn symptoms and stored in -80° freezer at our lab facility. These samples are labeled with a study code and will be used in our analysis (pseudonymized) to compare with healthy controls, and more severe GERD patients.

- Ussing chamber experiments

During ussing chamber experiments, 4 biopsies of GERD patients/healthy controls will be collected in PBS medium and asap mounted between 2 hemichambers. The chambers will be kept at optimal conditions using air infusion, and using Krebs buffer solution. The transepithelial electrical resistance (TEER) will be measured, and transepithelial flux of a fluorescent molecule, from mucosal to serosal site. The data are stored at the PC connected to the ussing chambers (txt), and saved in a personal folder with the study code number of the patient. The data will be transferred to an electronic calculation sheet, and the analyzed data will be kept in the file with the study code on KU Leuven one drive, only accessible by the investigators.

- pH-measurement

In order to assess the acid exposure time and number of reflux episodes in our patients (important for the diagnosis of GERD), we will perform pH-measurements in suspected GERD patients. TFor this measurement, a pH-probe is inserted in the esophagus of the patient, and the pH and impedance in the esophagus is recorded by the equipment on a memory card for 24 hours. After removal of the catheter, the data on the memory card are uploaded in a designated computer in the endoscopy room and saved on UZ data as .coo file and .soo file (shared folder), only accessible by nursing staff, the treating physicians, and investigators involved in the project. The analysis will be done using software of Sandhill applications. A report will be generated in a word file, this will be stored with the other patient data. The results will be pseudonymized and uploaded in the KU Leuven one drive coded (study code) file, only accessible by the investigators.

- Esophageal manometry

In a subset of patients and healthy controls, esophageal manometry will be performed. A catheter with several pressure sensors will be inserted through the nose in the esophagus, and pressure waves in the esophagus will be followed during swallows. For the analysis we use MMS (Medtronic) provided software. The data will be stored on KU Leuven one drive after pseudonimization in FCU format. A report will be generated in KWS, and will be used in our coded file (study code) in KU Leuven one drive.

- EndoFLIP measurement

In patients that underwent sleeve gastrectomy and developed GERD postoperatively, we will investigate the effectiveness of the STRETTA procedure. Before, and 6 months after the procedure, we will use EndoFLIP to assess the compliance of the lower esophageal sphincter. This measurement is analyzed by one of the investigators, and the data are stored in txt and excel format on UZ Leuven shared drive, in a password protected folder only accessible by the investigators and treating physicians. A report will be uploaded in KWS, in the electronic medical file of the patient. The result of the measurement will also be kept in the coded file of the study participant on the KU Leuven one drive.

- STRETTA procedure.

As discussed above, in patients with GERD post-sleeve gastrectomy, we will perform a stretta procedure in a sham controlled study. The procedure will be performed by the PI and a report will be uploaded in the electronic patient file (KWS). The results of the procedure (sham or real) will be uploaded in the coded study file of the patient on KU Leuven one drive, only after termination (and thus deblinding) of the investigator.

Specify in which way the following provisions are in place in order to preserve the data during and at least 5 years after the end of the research? Motivate your answer. (use up to 700 characters)

1. Designation of responsible person (If already designated, please fill in his/her name.)
2. Storage capacity/repository
    - during the research
    - after the research

The responsible persons for this project are the two promotors: prof. dr. Jan Tack and prof. dr. Tim Vanuytsel. Both staff members of the department of Gastroenterology and Hepatology, and PI's at our lab at TARGID. Prof. Tack will be retiring in 6 years, so within the 5 years after termination of this project. However, Tim Vanuytsel will still be a member of the staff at that time, and data will thus be available to him.
All of the data gathered contains only a limited data volume, the available storage at KU Leuven One Drive, UZ data, and KWS will be enough for complete data storage.
Since this is a project with a highly heterogeneous study population, with only limited amounts of participants, we do not plan to share/publish them at this stage.

What's the reason why you wish to deviate from the principle of preservation of data and of the minimum preservation term of 5 years? (max. 700 characters)

I do not wish to deviate.

Are there issues concerning research data indicated in the ethics questionnaire of this application form? Which specific security measures do those data require? (use up to 700 characters)

This project will handle with vulnerable personal/medical data on patients and healthy volunteers. As described above, these data will only be identifiable at UZ Leuven data and the electronic medical record of the patients (KWS). These are only accessible by treating physicians and medical staff. The data that will be stored on KU Leuven one drive will be pseudonymized before storage, and the study code will be kept in a seperate folder, only accessible by the investigators.
The majority of the protocols which are used in this project are already approved by the Ethical Committee at KU Leuven (S63184, S64212, S61111). For an additional study in patients and helathy volunteers, using the multimodal stimulation protocol with or without lidocain infusion in a double blind cross-over fashion, a protocol will be submitted to the ethical committee in the coming year.

Which other issues related to the data management are relevant to mention? (use up to 700 characters)

no additional comments.

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DPIA

DPIA

Have you performed a DPIA for the personal data processing activities for this project?

- Not applicable

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GDPR

GDPR

Have you registered personal data processing activities for this project?

- Yes
- Yes

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FWO DMP (Flemish Standard DMP)

1. Research Data Summary

List and describe all datasets or research materials that you plan to generate/collect or reuse during your research project. For each dataset or data type (observational, experimental etc.), provide a short name & description (sufficient for yourself to know what data it is about), indicate whether the data are newly generated/collected or reused, digital or physical, also indicate the type of the data (the kind of content), its technical format (file extension), and an estimate of the upper limit of the volume of the data.

				Only for digital data	Only for digital data	Only for digital data	Only for physical data
Dataset Name	Description	New or reused	Digital or Physical	Digital Data Type	Digital Data format	Digital data volume (MB/GB/TB)	Physical volume
		Please choose from the following options: • Generate new data • Reuse existing data	*Please choose from the following options:* • Digital • Physical	*Please choose from the following options:* • Observational • Experimental • Compiled/aggregated data • Simulation data • Software • Other • NA	*Please choose from the following options:* • .por, .xml, .tab, .cvs,.pdf, .txt, .rtf, .dwg, .gml, … • NA	*Please choose from the following options:* • <100MB • <1GB • <100GB • <1TB • <5TB • <10TB • <50TB • >50TB • NA	
Questionnaires	online questionnaires will be answered in qualtrics, data will be extracted in excel files	new	digital	observational	.cvs	<100GB	
Medical history	Relevant medical history data organized in question/answer style (eg: age? 25y)	New	Digital	observational	.cvs	<1GB	
Upper endoscopy results	Included in data file with medical history in question/answer style	New	Digital	interventional	.cvs	<1GB	
Multimodal esophageal stimulation	Results will be noted in a structured file in question/answer style (eg. amount of minutes for first sensation: 5 min)	New	Digital	interventional	.cvs	<1GB	
Biopsy collection	Esophageal and duodenal biopsies will be stored in -80°C freezers until further analysis	New	physical	interventional			80 bopsies in OCT (2x2cm), 80 biopsies in epjes (1.5mL), 40 paraffine blocks
Esophageal biopsies	Esophageal biopsies that were collected during a previous project will be used to make coupes for immunohistochemistry	Reused	physical	interventional			42 paraffine blocks
Ussing chamber experiments	4 esophageal biopsies will be mounted in ussing chambers to assess ex-vivo permeability	New	Digital	interventional	.cvs	<1GB	
pH-impedance measurement	as part of clinical routine, pH-impedance measurements will be collected in patients with typical GERD symptoms	New/Reused (if this was already done as part of clinical practice)	Digital	interventional	.S01 (data file specifically generated by Bioview analysis for analysis of pH-impedance measurements)	<100GB	
Esophageal high resolution impedance manometry	Pressure measurement of esophageal peristalsis and lower esophageal sphincter	New/Reused (if this was already done as part of clinical practice)	Digital	interventional	.FCU (data file specifically for MMS esophageal manometry software)	<100GB	
EndoFLIP measurement	distensibility measurement of the lower esophagus and lower esophageal sphincter	New/Reused (if this was already done as part of clinical practice)	digital	interventional	.txt -> later analyzed in .cvs file.	<100GB	
Stretta procedure	in a subset of patients (specifically with GERD after sleeve gastrectomie) we will perform stretta anti-reflux procedure (endoscopically). The results of this procedure will be uploaded in KWS and kept in our digital data file	New	digital	interventional	.cvs	<1GB	

If you reuse existing data, please specify the source, preferably by using a persistent identifier (e.g. DOI, Handle, URL etc.) per dataset or data type:

only physical data will be reused, or data from KWS.

Are there any ethical issues concerning the creation and/or use of the data (e.g. experiments on humans or animals, dual use)? Describe these issues in the comment section. Please refer to specific datasets or data types when appropriate.

- Yes, human subject data

Will you process personal data? If so, briefly describe the kind of personal data you will use in the comment section. Please refer to specific datasets or data types when appropriate.

- Yes

sex
age
date of birth
medical and surgical medical history
results of diagnostic tests
(pseudonymised)

Does your work have potential for commercial valorization (e.g. tech transfer, for example spin-offs, commercial exploitation, …)? If so, please comment per dataset or data type where appropriate.

- No

Do existing 3rd party agreements restrict exploitation or dissemination of the data you (re)use (e.g. Material/Data transfer agreements/ research collaboration agreements)? If so, please explain in the comment section to what data they relate and what restrictions are in place.

- No

Are there any other legal issues, such as intellectual property rights and ownership, to be managed related to the data you (re)use? If so, please explain in the comment section to what data they relate and which restrictions will be asserted.

- No

2. Documentation and Metadata

Clearly describe what approach will be followed to capture the accompanying information necessary to keep data understandable and usable, for yourself and others, now and in the future (e.g., in terms of documentation levels and types required, procedures used, Electronic Lab Notebooks, README.txt files, Codebook.tsv etc. where this information is recorded).

The electronic database Sharepoint will be used to store data, where all involved researchers can find a clear overview of the data.
Study code numbers, date of inclusion/collection of the data will be clearly marked (for digital as well as physical data). The same study code will be used for both digital and physical data.
Physical data will be stored together per participant and per study protocol, clearly labeled with different colored stickers and with study code numbers, dates, and content of the collected material.
Digital data will be stored in a question/answer style, making it readible for involved/future researchers.
Data files will be pseudonimized and the study code numbers will be kept seperately in a clearly marked file (.csv).

Will a metadata standard be used to make it easier to find and reuse the data? If so, please specify (where appropriate per dataset or data type) which metadata standard will be used. If not, please specify (where appropriate per dataset or data type) which metadata will be created to make the data easier to find and reuse.

Metadata will be created manually where appropriate (per study participant, per collected data). It will be used to describe date and time of data capturing, coding of questions in database questionnaires. A clear description of what the data respresents and how it was generated will be provided, including a description of materials, methodology design, setup and parameters.

3. Data storage & back-up during the research project

Where will the data be stored?

- Sharepoint will be used for digital data entering and storage (medical history, results of diagnostic tests,...)
- Other digital data will be stored in KU Leuven onedrive in a folder only accessible to the involved researchers

How will the data be backed up?

KU Leuven onedrive and Sharepoint are secured and backed-up by the ICTS service of KU Leuven.

Is there currently sufficient storage & backup capacity during the project? If yes, specify concisely.
If no or insufficient storage or backup capacities are available, then explain how this will be taken care of.

- Yes

Sufficient storage & backup capacity is provided by the KU Leuven during and after the project.

How will you ensure that the data are securely stored and not accessed or modified by unauthorized persons?

The folders/Redcap will only be accessible by involved researchers (pasword/login protected).

What are the expected costs for data storage and backup during the research project? How will these costs be covered?

KU Leuven provides online storage using Sharepoint for free up to 5TB, this will be sufficient for this research project.

4. Data preservation after the end of the research project

Which data will be retained for at least five years (or longer, in agreement with other retention policies that are applicable) after the end of the project? In case some data cannot be preserved, clearly state the reasons for this (e.g. legal or contractual restrictions, storage/budget issues, institutional policies...).

All data will be preserved for 10 years according to KU Leuven RDM policy.
Data that were created in a project with medicinal products (eg. citalopram study) will be kept for 25 years.
All data that are at the basis of publications will be kept and preserved for 25 years.
Data that is likely to be reused within the research unit will also be preserved longer than 10 years.

Where will these data be archived (stored and curated for the long-term)?

- Where appropriate (published data), dedicated data repositories will be considered for storage and data sharing (upon request).
- Physical data will be stored at TARGID/ Biobank where appropriate.
- Other digital data will be stored in KU Leuven onedrive, with a back-up on a harddrive on site, only accessible to researchers involved in the project.

What are the expected costs for data preservation during the expected retention period? How will these costs be covered?

KU Leuven provides storage and back-up using Sharepoint for free up to 5TB, this will be sufficient for this research project.

5. Data sharing and reuse

Will the data (or part of the data) be made available for reuse after/during the project? In the comment section please explain per dataset or data type which data will be made available.

- Yes, in a restricted access repository (after approval, institutional access only, …)
- Yes, in an Open Access repository

available upon request.

If access is restricted, please specify who will be able to access the data and under what conditions.

We have no data transfer agreements for this project.

Are there any factors that restrict or prevent the sharing of (some of) the data (e.g. as defined in an agreement with a 3rd party, legal restrictions)? Please explain in the comment section per dataset or data type where appropriate.

- No

Where will the data be made available? If already known, please provide a repository per dataset or data type.

not known yet.
This depends on where we would like to publish our data.
KU Leuven RDR is a candidate if no other specific database is appropriate.

When will the data be made available?

After publicaton.

Which data usage licenses are you going to provide? If none, please explain why.

We will follow the guidelines provided by KU Leuven RDR.

Do you intend to add a PID/DOI/accession number to your dataset(s)? If already available, you have the option to provide it in the comment section.

- Yes

What are the expected costs for data sharing? How will these costs be covered?

The budget will cover storage costs and long-term preservation costs.

6. Responsibilities

Who will manage data documentation and metadata during the research project?

Karlien Raymenants

Who will manage data storage and backup during the research project?

Karlien Raymenants

Who will manage data preservation and sharing?

Karlien Raymenants during the project, prof. Jan Tack and Tim Vanuytsel after this PhD project.

Who will update and implement this DMP?

Karlien Raymenants