PICCOLO

Multimodal highly-sensitive PhotonICs endoscope for improved in-vivo COLOn Cancer diagnosis and clinical decision support

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Abstract:

This document is the last version of Deliverable ”Ethical use of data in health databases” (D7.7) that includes the activities belonging to task 7.3.

D7.7 includes the Data Management Plan (DMP) for the PICCOLO project to assure a proper use of all generated data in accordance with the Guidelines of FAIR Data Management in Horizon 2020.

Dissemination level		
PU	Public	X
CO	Confidential, only for members of the consortium and the Commission Services	

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Documents history

Document version #	Date	Change
V0.1	29/05/2019	Integrated version (sent to WP members)
V0.2	25/06/2019	Definition of ToC
V0.3	25/06/2019	First complete draft
V0.4	15/07/2019	Integrated version (send to WP members)
V0.5	15/07/2019	Updated version (send to Quality Manager)
V0.5	15/07/2019	Updated version (QM send to project internal reviewers)
V0.6	18/07/2019	Reviewed version sent to QM
Sign off	18/07/2019	Signed off version (for approval to EB members)
V1.0	19/07/2019	Approved Version to be submitted to H2020 office

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Executive summary

Work package 7 (WP7) focuses on the ethical, legal, regulatory and safety issues associated to the development of the PICCOLO diagnosis medical device that will accelerate the road to market process in an ethical and safe way.

Data Management plans (DMPs) are a key element for a good data management. A DMP describes the data management life cycle for the data to be collected, processed and/or generated by a Horizon 2020 project. As part of making research data findable, accessible, interoperable and re-usable (FAIR), a DMP should include information on:

- The handling of research data during and after the end of the project;
- What data will be collected, processed and/or generated;
- Which methodology and standards will be applied;
- Whether data will be shared/made open access;
- How data will be curated and preserved (including after the end of the project).

The definition, analysis and evaluation of the ethical use of health data described in T7.3 are gathered in this document. For this aim, the FAIR Guidelines Guideline on FAIR Data Management in Horizon 2020 described in D7.1 and D7.4 have been followed.

This deliverable is the last version of PICCOLO Project's DMP. At this stage of the project all ethical aspects are solved, although there is not an agreement on how data would be made open access. Despite this, this document recalls different feasible scenarios for making data open accessible which will be discussed and decided by Project Consortium and if agreed executed just before the end of the project. All related relevant documents are already developed (See Annexes).

1. Introduction

1.1 Objective of this document

The objectives of this document are to:

- Gather all the ethical aspects related to the definition and evaluation of proper use of all generated databases during the PICCOLO project according the Guideline on FAIR Data Management in Horizon 2020.
- Provide a final guidance of the ethical use of data in the project databases processed during the project that will benefit both the medical and wider research communities.

This version of the deliverable includes main ethical aspects agreed among the consortium members at this stage of the project.

1.2 Structure of this document

This document, is structured based on the set of questionnaires listed in the Guideline on FAIR Data Management in Horizon 2020. The first section introduces the document and explains its aims in the context of related deliverables from other WPs. The second section describes the ***health data*** used in the PICCOLO project. The third and fourth section list a set of questions related to the management of the datasets in a findable, accessible, interoperable and reusable (FAIR) way. The fifth section is about the data security issues and the last section gathers ethical aspects that should be taken into account throughout the project.

1.3 Relationships with other deliverables

Since the early stages of the project, PICCOLO gives special attention to identify and monitor the particular challenges related to ethical issues associated to the development of the PICCOLO medical device.

D7.7 will directly be related to the following deliverables:

- D3.1 Image Database acquisition protocol
- D3.2 Photonic (Wide–Field + Oct + MPT) Database (v1)
- D3.5 Photonic (Wide–Field + Oct + MPT) Database (v2)
- D5.1 Validation plan on animal models
- D5.2 Laboratory tests report
- D5.3 System validation & evaluation report on animal models (v1)
- D5.4 System validation & evaluation report on animal models (v2)
- D6.1 Human tissue validation plan
- D6.2 System validation & evaluation report on human tissues
- D7.1 Ethical, regulatory and DMP protocols and copies of the ethical approvals of the competent national/local committees/bodies
- D7.2 Ethical and regulatory dialogues and minutes (v1)
- D7.3 Safety, efficacy criteria and patient risks report (v1)

- D7.4 Ethical use of data in health databases (v1)
- D7.5 Ethical and regulatory dialogues and minutes (v2)
- D7.6 Safety, efficacy criteria and patient risks report (v2)
- D7.8 Ethical and regulatory dialogues and minutes (v3)
- D7.9 Safety, efficacy criteria and patient risks report (v3)
- D10.1 H-POPD – Requirement No. 1 (Ethical requirements)
- D10.2 HCT-A – Requirement No. 2 (Ethical requirements)

1.4 Acronyms and abbreviations

.mxf	Material Exchange Format
D	Deliverable
DICOM	Digital Imaging and Communication in Medicine
DMP	Data Managment Plan
DPD	Data Protection Delegate
EB	Executive Board
EthC	Ethical Committee
FAIR	Findable, Accessible, Interoperable and Reusable
FTP	File Transfer Protocol
GA	General Assembly
GB	Gigabyte
H&E	Hematoxylin and Eosine
JSON	JavaScript Object Notation
MB	MegaByte
MPT	Multi-photon tomography
NBI	Narrow Band Imaging
OCT	Optical coherence tomography
OME	Open Microscopy Environment
PPIF	Post-project impact follow-up Committee
WP	Work Package
XML	Extensible Markup Language

2. Data Summary

2.1 Description

2.1.1 What is the purpose of the data collection/generation and its relationship to the objectives of the project?

The main objective of the project is to develop a new compact, hybrid and multimodal photonics endoscope based on Optical Coherence Tomography (OCT) and Multi-Photon Tomography (MPT) combined with novel red-flag fluorescence technology for in-vivo diagnosis and clinical decision support. This endoscope will include a Computer Aided Diagnosis (CAD) System module that will endow the photonics endoscope with optical biopsy capabilities for in-situ polyp characterization, lesion infiltration assessment and remaining resection tissue assessment.

Therefore, for this purpose the PICCOLO project will produce an extensive digital database of images representing colonic neoplasic and hyperplasic lesions together with healthy tissues. The necessity of generating a stratified and fully annotated digital database for the identification and validation of the imaging biomarkers in the project will provide unprecedented information on OCT and MPT imaging. This information will serve the research community as a boost for OCT/MPT imaging biomarkers discovery, analysis of the capabilities of OCT/MPT technology for diagnosis, further analysis on clinical prognosis related to the OCT/MPT biomarkers, and lesion grading studies among others.

Wide field recordings and images from animal model will be also stored in the database. These will allow for tracking of lesion development, which is currently not feasible in human patients.

2.1.2 What types of formats of data will the project generate/collect?

OCT/MPT imaging data will follow lossless standard formats such as DICOM or conventional lossless image compression with associated JSON format for metadata. Histology imaging will be comprised of lossless OME (open microscopy environment) standard (OME-JPEG) and metadata will be offered in standard XML format. DAPI dataset will be included in standard format in a similar way as BIOPOOL project.

Wide field recordings will be stored in lossless compressed frames that include a JSON for the associated metadata. Hyperspectral wide field recordings will be stored in ENVI format which is supported by lots of external libraries and open software.

2.1.3 Will you re-use any existing data and how?

Existing data that was generated in the project BIOPOOL FP7 has been re-used in the PICCOLO project. BIOPOOL FP7 project constructed a digital repository of digital histology that allows researchers to access histological data. Innovative software was developed to search and gather digital pathology slides with associated data from multiple biobanks and pathology archives. The software is based on an innovative Content-Based Image Retrieval system. BIOEF (Project Coordinator) and TECNALIA (Technical Coordinator) were partners in this project and have an outsourcing contract that allows TECNALIA to use data generated by BIOEF. The necessary approvals from the Basque Country Ethics

Committee for using these data in PICCOLO Project have been obtained (Explained in detail in Section 6.1.2).

2.1.4 What is the origin of the data?

The database will contain datasets with different origins:

- Imaging database of murine model (healthy and diseased): ~50 samples
- Stratified imaging database of murine model (healthy and diseased): ~400 samples
- Imaging database of human samples (healthy and diseased): ~400 samples
- Database of wide field colonoscopy videos of human samples: ~50 samples
- Database of wide field colonoscopy videos of murine model: ~100 samples
- Autofluorescence DAPI microscopy images database of murine model: ~280 samples
- Autofluorescence DAPI microscopy images database of human model: ~20 samples

The sample size estimates can vary as data still is being collected.

The PICCOLO database will contain the following datasets:

- Imaging database of murine model (healthy and diseased): This dataset will contain imaging data from wide field, OCT and MPT imaging systems of genetically modified murine models. This set of data will contain specific trials related to model the degradation of the acquired signal during the biopsy tissue processing protocol. It will be performed in order to check if the biopsied sample is in the best condition (from fresh to ready-to-histopathology stage) to be analyzed suffering the minimum possible changes in structural and functional characteristics. After imaging, data will be acquired; conventional histopathological analysis will be performed over the tissue to serve as gold standard. Metadata on each acquired image and its acquisition conditions will also be included (~50 samples).

- Stratified imaging database of murine model (healthy and diseased): This dataset will contain ex-vivo and in vivo wide field and OCT/MPT imaging data from stratified murine model obtained during laparotomy. After imaging, data will be acquired; conventional histopathological analysis will be performed over the tissue to serve as gold standard. Due to the temporal precision of murine models for developing neoplastic lesions, this database will offer a stratified lesion grading to the database. This dataset will include wide field, OCT and MPT images of each sample, their corresponding high resolution histological microscopy images (provided by BIOEF) and the anatomopathological diagnosis report including lesion grading. This will serve researchers to analyze the limits of the technology and to enhance imaging biomarkers to allow early diagnosis (100 subjects/~400 samples).

- Imaging database of human samples (healthy and diseased): This dataset will contain data from real patients included in the WP6 studies and will be performed under strict ethical and safety conditions defined in WP7. Thus, all the human tissue images and metadata associated will be collected once signed, informed consent is provided by the patient (Explained in detail in Section 6.1.2). The data will include ~ 400 wide field and OCT/MPT imaging data gathered immediately after tissue resection. Comparative histology high resolution microscopic imaging will be included as well as pathological diagnosis report.

- Database of wide field colonoscopy videos of human samples: This dataset will contain data from real patients and will be performed under strict ethical and safety conditions. Thus, all the video will be collected once signed, informed consent is provided by the patient (see annex 4). It will include videos collected during routine colonoscopy procedures in order to analyze polyp optical detection. It has been estimated 50 cases/videos as a first stage, if it is necessary more cases will be captured.

- Database of wide field colonoscopy videos of murine model: This dataset will contain data from wide field videos of murine models collected during colonoscopy or laparotomy procedures. It has been estimated 100 videos as a first stage. If it is necessary, more videos will be captured.

- Autofluorescence DAPI microscopy images database of murine model: This dataset will contain data from autofluorescence DAPI microscopy images of murine models. It will include images from hyperplasic and neoplastic polyps after and before H&E staining. A histopathological diagnosis will be performed for each sample including a digitalized scan image of the H&E stained sample and a Histopathological Report (~140 samples, 2 DAPI images per sample, ~280 DAPI images, ~ 140 H&E images).

- Autofluorescence DAPI microscopy images database of human model (health and diseased): This dataset will contain data from autofluorescence DAPI microscopy images of human models. It will include images from hyperplasic and neoplastic polyps after and before H&E staining. A histopathological diagnosis will be performed for each sample including a digitalized scan image of the H&E stained sample and a Histopathological Report (~20 samples).

A more exhaustive description of these databases: content, acquisition, ethical aspects and other considerations can be found in Deliverable D3.2, due by Month 30. Next versions of this deliverable (D3.5) will contain content updates of collected data.

The following two tables below (Table 1a and Table 1b) show the metadata that will be associated to the images captured with the PICCOLO device from murine samples and those for specific safety and tissue degradation trials.

Table 1a. Data associated to images obtained from murine samples

MURINE METADATA	
CODE	SAMPLE ID_SAMPLE_ORIGIN_ID_MODALITY
SAMPLE_ID	ID stating the acquisition identification to map sample among different imaging modalities.
SAMPLE_ORIGIN_ID	ID indicating the source of the tissue (rat) [1]
SEX	Male/Female
GROUP	G0 – control, G1 – hyperplasic, G2 – Neoplastic 2 months, G3 – Neoplastic 4 months, G4 – Neoplastic 8 months
SAMPLE STATE	In-vivo, Ex-vivo-fresh, Ex-vivo-paraffin
COLONOSCOPY DATE_TIME	DD/MM/YYYY
FOLLOW-UP NUMBER	
IMAGING MODALITY	Wide field / MPT / OCT / H&E Histopathology/ METADATA
POLYP SIZE	(mm)
POLYP LOCALIZATION	Ascending colon/Transverse colon/Descending colon/Sigmoid colon/Rectum
KUDO´S PIT PATTERN	Non-neoplastic: I, II Non-invasive: IIIs, IIIL, IV Invasive pattern: Vi, VN
PARIS CLASSIFICATION	Protruded lesions: Ip, Ips, Is Flat elevated lesions: 0-IIa, 0-IIa/c Flat lesions: 0-IIb, 0-IIc, 0-IIc/a
NICE CLASSIFICATION (NBI Vascular pattern)	Type 1, Type 2, Type 3
MORPHOLOGIC DIAGNOSIS	SNOMED Code
TOPOGRAPHIC DIAGNOSIS	SNOMED Code
LITERAL DIAGNOSIS	
HISTOLOGICAL STRATIFICATION	No dysplasia/Low grade dysplasia/High grade dysplasia/Invasive adenocarcinoma/Hyperplasia/Serrated morphology
ADDITIONAL FINDINGS	

[1] Murine specimens will be identified with a unique ID. This code will be used to trace the origin of the sample if required and for the definition of the training and test sets during the evaluation of the algorithms to be developed in WP3.

Table 1b. Data associated to specific safety and tissue degradation trials

MUCOSA LAYER
Ulceration of mucosal epithelium
Infiltrate of neutrophils/eosinophils in lamina propria
Infiltrate of lymphocytes, macrophages or fibrosis of the lamina propria
Edema in lamina propria
Vascular changes in lamina propria
Crypt hyperplasia
Crypt dilation
Globet cells changes
SUBMUCOSA LAYER
Infiltrate of neutrophils/eosinophils
Infiltrate of mononuclear cells/fibrosis
Vascular changes of the submucosa layer
Edema in submucosa layer
MUSCULAR LAYER
Infiltrate of neutrophils/eosinophils
Infiltrate of lymphocytes, macrophages or fibrosis
Edema
Infiltration of cells in the serosa layer

The score ranged from:

0 (No change): when no injury was observed, or changes were within the normal range;
1 (Minimal): when changes were sparse but exceeded those considered normal;
2 (Slight): the lesion is easily identified but of limited severity;
3 (Moderate): The lesion is prominent, but there is significant potential for increased severity;
4 (Severe): The degree of change is as complete as possible (occupies the majority of the analyzed tissue).

The maximum injury SCORE is 48 in the case of endoscopic biopsies and 64 in the entire wall thickness.

In addition, samples from animals of Phase 1 (Validation) will be classified as healthy, hyperplasia or neoplasia. In case of neoplasia, the infiltration grade will be assessed.

The table below (Table 2) shows the metadata that will be associated to the images captured with the PICCOLO device from human samples:

Table 2. Data associated to images obtained from human samples

HUMAN METADATA	
CODE	SAMPLE ID_SAMPLE_ORIGIN_ID_MODALITY
SAMPLE_ID	ID stating the acquisition identification to map sample among different imaging modalities.
SAMPLE_ORIGIN_ID	Anonymized ID indicating the source of the tissue (patient) [2]
AGE	(years)
SEX	Men/Women
IMAGING MODALITY	Wide field / MPT / OCT / H&E Histopathology/ METADATA
REASON FOR COLONOSCOPY	Screening colonoscopy/Urgent colonoscopy for altered bowel habit/Surveillance/therapy
COLONOSCOPY DATE_TIME	DD/MM/YYYY
NUMBER OF FOUND POLYPS	
POLYP SIZE	(mm)
POLYP LOCALIZATION	Ascending colon/Transverse colon/Descending colon/Sigmoid colon/Rectum
KUDO´S PIT PATTERN	Non-neoplastic: I,II Non-invasive: IIIs, IIIL, IV Invasive pattern: Vi, VN
PARIS CLASSIFICATION	Protruded lesions: Ip, Ips,Is Flat elevated lesions: 0-IIa, 0-IIa/c Flat lesions: 0-IIb, 0-IIc, 0-IIc/a
NICE CLASSIFICATION (NBI Vascular pattern)	Type 1, Type 2, Type 3
BOSTON BOWEL PREPARATION SCALE	0, 1, 2, 3
MORPHOLOGIC DIAGNOSIS	SNOMED Code

[2] Patients will be identified with a unique ID defined exclusively for the project. From this ID, it won't be possible to identify the patients or access any information of them. Only clinicians at IC and BIOEF will know the real patient information under this codified ID. In this respect, the European regulation on general data protection (Regulation (EU) 2016/679) will be applied. Since the implementation date of this new regulation is the 25 of May 2018, until then, current directive on data protection (95/46/EC) will be followed.

TOPOGRAPHIC DIAGNOSIS	SNOMED Code
LITERAL DIAGNOSIS	
HISTOLOGICAL STRATIFICATION	No dysplasia/Low grade dysplasia/High grade dysplasia/Invasive adenocarcinoma/Hyperplasia/Serrated morphology
PREVIOUS TREATMENT	Yes/No
RECURRENCE	Yes/No
ADDITIONAL FINDINGS	

2.1.5 What is the expected size of the data?

The following table contains a brief summary of the expected data size at this stage of the project.

Description	Number of samples	Expected size	Type
Imaging database of murine model	~50 samples MPT/OCT images Associated histological data	 10-30 image acquisition/sample., 10MB/3D OCT + MPT image < 15GB 50 samples x 300Mb/each sample < 15GB	 Uncompressed 16bit images. For quality purposes only JPG2000
Stratified imaging database of murine model	~400 samples MPT/OCT images Associated histological data	 10-30 image acquisition/sample., 10MB/3D OCT + MPT image < 120GB 400 samples x 300Mb/each < 120GB	 Uncompressed 16bit images. For quality purposes only JPG2000
Imaging database of human samples	~400 samples MPT/OCT images Associated histological data	 10-30 image acquisition/sample., 10MB/3D OCT + MPT image < 120GB	 Uncompressed 16bit images. For quality purposes only JPG2000

		400 samples x 300Mb/each < 120GB	
Associated clinical text data	~400 samples	100MB	JSON based data
Human colonoscopy videos	~50 samples	50GB, ~10min/sample	Annotated videos
Murine models colonoscopy videos	~100 samples	480MB, ~2min/video	Annotated videos
Associated clinical text data (video)	~50 samples	50GB, ~10min/sample	Annotated videos
Autofluorescence DAPI microscopy images database of murine model	~280 samples DAPI Images Associated histological data	2GB/sample	Uncompressed 16bit images. For quality purposes only JPG2000
Autofluorescence DAPI microscopy images database of human model	~280 samples DAPI Images Associated histological data	2GB/sample	Uncompressed 16bit images. For quality purposes only JPG2000

Note: The sample sizes of each of the datasets are estimates based on the initial schedule for the availability of the developed prototype. The delays in the release of the device can and will affect to achieve the expected sample size, especially for human models (very time dependant). The time for data collection will be reduced at least in a half for human models. As commented before updates on Photonic (Wide-Field + OCT + MPT and DAPI) Databases can be found in following versions of D3.2 (D3.5).

2.1.6 To whom might the data be useful ('data utility')?

As a first stage, the dataset created in the PICCOLO project might be useful mainly for researchers and developers of the project, as well as for consortium members with clinical profiles. The detailed data sharing among the members would allow the development of the Multimodal highly-sensitive PhotonICs endoscope, PICCOLO's final product.

At the end of the project, PICCOLO Consortium has agreed on creating an Open digital repository of the digital database of colon neoplastic and hyperplasic lesions generated during the project. During the development of the project this data will be used by Consortium members, researchers and developers of the project for the identification and validation of the imaging biomarkers in the project. Moreover, the final open digital repository will serve research communities as a boost for OCT/MPT imaging biomarkers discovery, analysis of the capabilities of OCT/MPT technology diagnosis, further analysis on diagnostic capabilities related to the OCT/MPT images, and lesion grading studies among colorectal polyps.

For this purpose, in order to ensure the right use of human data (images and associated minimum clinical data) a risk assessment and impact evaluation is being carried out by an external legal agency (see annex 5). This will be notified to the Basque Ethics Committee before the end of the project.

3. FAIR data

3.1 Making data findable, including provisions for metadata

3.1.1 Are the data produced and/or used in the project discoverable with metadata, identifiable and locatable by means of a standard identification mechanism (e.g. persistent and unique identifiers such as Digital Object Identifiers)?

The files exchanged in the PICCOLO project will be uniquely identifiable and versioned by using the following naming convention (based on the institutions where images are collected). This will help tracing the origin/source of the data:

- PICCOLO_CCMIJU_ YYYY-MM-DD_#CODE
- PICCOLO_IC_YYYY-MM-DD_#CODE
- PICCOLO_BIOEF_YYYY-MM-DD_#CODE

The term CODE is explained in detail in Table 3. The dataset will be stratified by SAMPLE_ID key. A SAMPLE_ID describes a single biological sample that belongs to a specimen identified as SAMPLE_ORIGIN_ID. A biological sample can be acquired by different modalities (Wide field, OCT, MPT, HISTOPATHOLOGY IMAGES or DAPI Images) and can also have related metadata.

Table 3. Labelling of entries in the PICCOLO Dataset

CODE: SAMPLE ID_SAMPLE_ORIGIN_ID_MODALITY	
SAMPLE_ID	ID stating the acquisition identification to map sample among different imaging modalities.
SAMPLE_ORIGIN_ID	Anonymized ID indicating the source of the tissue (patient)
MODALITY	White light / MPT / OCT / H&E Histopathology/ METADATA
MODALITY SPECIFIC METADATA	Specific metadata for each imaging modality

For machine learning purposes (in WP3) it is enough to provide the zipped dataset. For other uses (e.g. clinical), it will be assessed in a future stage of the project if search key-words will be provided in order to optimize the possibilities of re-use. At present, search keywords are out of the scope of the project and data will be shared as a zipped dataset.

Different versions of the database are subject to be created during the development of the multi-source endoscope. Each version of the endoscope will work with a different version of the database, as the database will growth exponentially during the development of the endoscope and the project. These database versions will be unequivocally identified and packaged. Each version generated will contain a file summarizing the samples contained.

3.1.2 What naming conventions do you follow?

Naming conventions have been detailed in WP3 at D3.1 and updated in D3.2. Details of the dataset will be included in a scientific publication at later stages of the project.

3.1.3 Will search keywords be provided that optimize possibilities for re-use?

See 3.1.2.

3.1.4 Do you provide clear version numbers?

See 3.1.2.

3.1.5 What metadata will be created? In case metadata standards do not exist in your discipline, please outline what type of metadata will be created and how.

Details of the dataset will be included in a scientific publication at later stages of the project and can be found in Deliverable D3.2 from WP3 and also listed in Section 2.1.4 of this document.

3.2 Making data openly accessible

3.2.1 Which data produced and/or used in the project will be made openly available as the default? If certain datasets cannot be shared (or need to be shared under restrictions), explain why, clearly separating legal and contractual reasons from voluntary restrictions.

At the end of the project, PICCOLO Consortium intends to make the data generated from murine and human samples openly available and it will be at the scientific community´s disposal. Data generated is listed in Section 2.1.4 of this document and described in more detail in D3.2 and further updates. There are no voluntary restrictions over human and murine data generated, although ethical issues for human tissue datasets are ruled by Spanish Royal Decree 1716/2011 of 18 November, which establishes the basic requirements for the authorization and operation of biobanks for biomedical research purposes and for the processing of human biological samples, and regulates the functioning and organization of the Spanish National Registry of Biobanks for biomedical research; and for sensible personal data, the Organic Law 3/2018, of December 5, “Protection of Personal Data and guarantee of digital rights”, modified according to the European Regulation on General Data Protection (Regulation (EU) 2016/679) will be applied and the Data Protection Delegate (DPD) at both institutions involved will be notified.

Additionally, scientific publications that are being produced during the development of the Project are being made open access (via project’s web site) when it doesn’t compromise any possible actual or future patents. With the aim of providing open access to peer-reviewed scientific publications that are and will result from the project, TECNALIA participates in Recolecta project (Open Science Harvester),

which is a platform that gathers all the Spanish scientific repositories together in one place and provides services to repository managers, researchers and decision-makers by following a 'Green' Open Access Model.

3.2.2 Note that in multi-beneficiary projects it is also possible for specific beneficiaries to keep their data closed if relevant provisions are made in the consortium agreement and are in line with the reasons for *opting out.*

Not Applicable.

3.2.3 How will the data be made accessible (e.g. by deposition in a repository)?

In the PICCOLO project, data will be generated in 3 different institutions:

- BIOEF: captured images and videos with the associated information will be stored at the Basque Biobank Database/BIOCLOUD (Central sample repository of the Basque Biobank-https://www.basquebiocloud.org/). The diagnosis of the colonoscopy as well as the anatomic pathology will also be transferred to the Basque Biobank Database/BIOCLOUD.
- Imperial College: Patient data, including any endoscopic images and histopathological reports, will be stored in secure servers controlled by Imperial College Healthcare NHS Trust, accessible by members of the IC research team.
- CCMIJU: Captured animal images with the associated information will be stored at the CCMIJU's internal structure of data storage.

During the project, all data generated in the PICCOLO project will be anonymized and transferred to a private repository to which PICCOLO partners will have access through security codes. All data will be aggregated at LENS facilities on a unique server for internal project work. Data exchanged among partners will be always encrypted. Moreover, in order to ensure the appropriate use of the data, the following logging message with the restrictions of use, as described in PICCOLO Consortium Agreement pag. 17, will be included:

a) protect and keep strictly confidential any part of/or the whole of any Confidential Information and shall treat and use the Confidential Information with the same degree of care as it applies to its own proprietary information, but in no case with less than reasonable care;
b) protect any part of/or the whole of the Confidential Information from disclosure to anyone other than their employees who have a need to know and inform them of the confidentiality attached to such Information;
c) not disclose, copy, duplicate totally or partially, unless extremely necessary for Purpose, the Confidential Information without the prior written consent of the Disclosing Party.

Use of the Confidential Information by the Receiving Party shall be strictly limited to the development of the Project.

The Receiving Party shall be responsible for the fulfillment of the above obligations on the part of their employees or third parties involved in the Project.

Once the project has ended, data generated from murine and human samples described in section 2.1.4 of this document will not remain any more in LENS facilities unique server. Data from human samples will be stored at the Basque Biobank Database/BIOCLOUD (Central sample repository of the Basque Biobank - https://www.basquebiocloud.org/). Regarding data form murine samples, the Consortium hasn't decided yet if it would be stored at the CCMIJU repository and/or in the European Open Science Cloud (EOSC; https://www.eosc-portal.eu/) which aims to create a trusted environment for hosting and processing research data to support EU science in its global leading role.

Six months before the end of the project the Post-project impact follow-up Committee (PPIF) will be officially formed. It will consist of members of the GA, EB and EthC and will be active for a limited period of time after the end of the project. (More information on the committee can be found in D9.1). This Board will be responsible of developing the guidelines for the Basque Biobank representatives to decide who can access data.

Data would ***ideally*** be made accessible by a specific request form that would be evaluated by the Basque Biobank representatives using the guidelines developed by the PPIF Committee

Information on the possibility of accessing the database generated and a link to the request form will be published in Websites belonging to the Basque Biobank (https://www.biobancovasco.org/) , own project website page (https://www.piccolo-project.eu/), and each partner's involved, including a brief description on the content available and instructions to access.

The request form will be designed and developed at the end of the project and information on data available and how to access it will be published in project and consortium member's websites. Request form will include, at least, the following information on the project that is requesting data:

1. Institution requesting data
2. Date
3. Responsible requesting data
4. Title of the Project
5. Abstract of the Project
6. Principal Investigator
7. Financial Entity
8. Duration
9. Beneficiaries
10. Ethics Committee Approval information

After Biobank representative decides, a formal letter will be sent to the responsible requesting data via email or postal mail answering the request including a short explanation. If agreed to make data accessible a standard Data Transfer Agreement will be signed between the solicitant and Biobank (as the owner of the data).

There are no ethical restrictions on animal data, but regarding data generated from human samples, a data protection impact assessment has been performed to evaluate the risk of identifying an individual

considering the provided variables associated to the images. As data susceptible of being made open access is not human tissue samples but human tissue images, the European Regulation on General Data Protection (Regulation (EU) 2016/679) should be applied instead of Royal Decree 1716/2011 of 18 November, which establishes the basic requirements for the authorization and operation of biobanks for biomedical research purposes and for the processing of human biological samples, and regulates the functioning and organization of the Spanish National Registry of Biobanks for biomedical research. Therefore, at the end of the project, once all human data generated is collected and specified, this report will be sent to the Basque Country ethical committee for its evaluation and approval making data generated from human samples openly accessible under the above restrictions at scientific community´s disposal.

If the Basque Country ethics committee considers that data should be ruled by the Royal Decree 1716/2011 of 18 November, which establishes the basic requirements for the authorization and operation of biobanks for biomedical research purposes and for the processing of human biological samples, and regulates the functioning and organization of the Spanish National Registry of Biobanks for biomedical research, this would change slightly the manner in which data would be made open accessible. It **would not** be immediate, after each favorable request evaluation a positive report from the Basque Country ethics committee should be reached before signing any Data Transfer Agreement and posterior sharing information.

3.2.4 What methods or software tools are needed to access the data?

The data will be made accessible through a webpage with access restriction. Access will be given by database owner after signing the documents designed for this purpose. Access will be provided via secure FTP. Activity logging will be included.

3.2.5 Is documentation about the software needed to access the data included?

N.A. as common image data and video formats will be used.

3.2.6 Is it possible to include the relevant software (e.g. in open source code)?

N.A. as common image data and video formats will be used.

3.2.7 Where will the data and associated metadata, documentation and code be deposited? Preference should be given to certified repositories which support open access where possible.

During the project for device developing purposes, as described in 3.2.3, all data generated along the project will be stored in each institution and at LENS facilities which will be a unique server for internal work of the consortium during the project lifetime.

At the end of the project, human data and associated metadata described in section 2.1.4 will be stored at the BIOCLOUD Repository in the Basque BIOBANK facilities. Deposit for murine data and metadata has still not been decided. There are several options, CCMIJU repositories and/or the European Open Science Cloud (EOSC) as commented in section 3.2.3 of this document.

3.2.8 Have you explored appropriate arrangements with the identified repository?

The arrangements are described in section 3.2.3.

During the following months the consortium members will deliberate and decide about it.

3.2.9 If there are restrictions on use, how will access be provided?

During the development of the project, access will be provided through security codes to the unique server for internal project work allocated at LENS facilities. Data exchanged among partners will be always encrypted.

Access to the publicly available data will be provided after Data Transfer Agreement contract signature as described in section 3.2.3.

3.2.10 Is there a need for a data access committee?

During the project lifetime, as included in the consortium agreement page 17, all the consortium members will follow the restrictions of data use.

At the end of the project, data access guidelines will be developed by the PPIF, which will be active for a limited period of time after the project. Basque Biobank Representative will evaluate the data request forms following these guidelines as described in section 3.2.3. of this document.

3.2.11 Are there well described conditions for access (i.e. a machine readable license)?

The request form will include all the conditions for accessing. The purpose and data use has to be included and it will be evaluated by the ethical committee in case of human data.

3.2.12 How will the identity of the person accessing the data be ascertained?

As described in section 3.2.3 of this document, the PPIF will develop data access guidelines which the Basque Biobank representative will follow to evaluate the data request form to access data. Moreover, the same process as already stored data in BIOCLOUD repository will be followed.

3.3 Making data interoperable

3.3.1 Are the data produced in the project interoperable, that is allowing data exchange and re-use between researchers, institutions, organizations, countries, etc. (i.e. adhering to standards for formats, as much as possible compliant with available (open) software applications, and in particular facilitating re-combinations with different datasets from different origins)?

PICCOLO project uses standard vocabularies for all data types present in the data set to allow inter-disciplinary interoperability. This will allow data exchange and re-use between researchers, institutions, organizations, countries, etc.

3.3.2 What data and metadata vocabularies, standards or methodologies will you follow to make your data interoperable?

Each published dataset will be clearly described on a scientific paper. Standard open json description files will be used. Standard image format will be used as detailed in section **¡Error! No se encuentra el origen de la referencia.**.

3.3.3 Will you be using standard vocabularies for all data types present in your data set, to allow inter-disciplinary interoperability?

See 3.3.2.

3.3.4 In case it is unavoidable that you use uncommon or generate project specific ontologies or vocabularies, will you provide mappings to more commonly used ontologies?

SNOMED codes are used for disease description. Specific ontologies will be described on the corresponding scientific paper.

3.4 Increase data re-use (through clarifying licenses)

According to the data sharing procedure agreed among the Piccolo Consortium members, this do not consider increasing the re-use of data through clarifying licenses or any other way.

Data is going to be made open accessible through a request form that must be approved and later a signature of a Data Management Agreement between claimer and sharer. This will allow exclusively the claimer the use of data, not being able to share it to third parties. If a third party is interested in accessing data, it must start de whole process again. Filling the request form out, sending it to the Basque Biobank, waiting for approval and finally signing the Data Management Agreement.

3.5 How will the data be licensed to permit the widest re-use possible?

Data will be licensed in the same way as already existing data is in BIOCLUD Repository.

3.5.1 When will the data be made available for re-use? If an embargo is sought to give time to publish or seek patents, specify why and how long this will apply, bearing in mind that research data should be made available as soon as possible.

It will be at the disposal of the scientific community and other interested parties after data validation and publication of the dataset informative scientific paper after the end of the project. The PPIF committee will establish an embargo time for each dataset generated within PICCOLO project to protect the exploitation strategy of the European companies in the project. This embargo time will be at least of 6 months after the end of the project for the partners to review data available and decide which would be the implications for each of them of data being open accessible. If there are, a new embargo period for the different datasets will be established.

3.5.2 Are the data produced and/or used in the project useable by third parties, in particular after the end of the project? If the re-use of some data is restricted, explain why.

Data produced in the project is usable by third parties after the end of the project. The terms for this reuse and restrictions are described in section 3.2.3 of this document.

3.5.3 How long is it intended that the data remains re-usable?

As BIOCLPOUD is a permanent repository, data will be remain re-usable for an unlimited time.

3.5.4 Are data quality assurance processes described?

See section 3.1.

4. Allocation of resources

4.1.1 What are the costs for making data FAIR in your project?

The total costs for making data FAIR have not been calculated at this stage of the project. However, just the tasks related to the Health Data Risk Assessment needed budget redistribution.

4.1.2 How will these be covered? Note that costs related to open access to research data are eligible as part of the Horizon 2020 grant (if compliant with the Grant Agreement conditions).

Full information of the new reallocation action mentioned in 4.1.1 was included in the amendment of the project.

4.1.3 Who will be responsible for data management in your project?

The owner of the data will be the clinical institution where the data have been collected. Then, considering that a copy of the data will be stored in the clinical institution where data have been collected and another in a repository physically located at LENS, the responsible for the management of each database will be the hosting institution during the development of the project.

At the end of the project murine and human data will be allocated at Basque Biobank repositories which will be responsible for data management after the end of the project.

4.1.4 Are the resources for long term preservation discussed (costs and potential value, who decides how and what data will be kept, and for how long)?

It has been decided to store data in the BIOCLOUD Basque Biobank repository. For terms of access data please see section 3.2.3 of this document. It has been decided to store data in the BIOCLOUD Basque Biobank repository. For terms of access data please see section 3.2.3 of this document.

5. Data security

5.1.1 What provisions are in place for data security (including data recovery as well as secure storage and transfer of sensitive data)?

The data generated in the PICCOLO project will be stored in secure repositories for long term preservation and curation. Regular backups (at least weekly) will be done for data security. The institution hosting the databases will manage these backups.

Secure passwords will be used for accessing the databases. Logs will be automatically generated in order to keep trace of the actions performed by each user. Access to the data will be only possible for the personnel directly involved in the project. As described in 3.2.3, a logging message will remind to the partners the right use of the data.

Data exchanged between the partners will be always encrypted and secured.

5.1.2 Is the data safely stored in certified repositories for long term preservation and curation?

The data generated in the PICCOLO project will be safely stored in regularly backed-up secure databases. The created databases allow for a long term preservation of data. The duration of the preservation of data is unlimited as it will be stored at the Basque Biobank repository BIOCLOUD.

6. Ethical aspects

6.1.1 Are there any ethical or legal issues that can have an impact on data sharing? These can also be discussed in the context of the ethics review. If relevant, include references to ethics deliverables and ethics chapter in the Description of the Action (DoA).

Personal data obtained in this project will be stored following the legal framework about data protection at national and European level. In this regard, dedicated servers will allow PICCOLO users to connect at once under controlled access. Personal data will be stored anonymized and only the research physicians (who maintain the contact with the patient) will know the identity of the patients.

Data will be kept indefinitely as long as it is not used in connection with decisions affecting particular individuals, or in a way that is likely to cause damage or distress to the patients.

The corresponding Data Protection Delegate (DPD) at BIOEF and Imperial College Healthcare NHS Trust will be notified according to the Data Protection Directive (EC Directive 95/46) and the European regulation on general data protection (Regulation (EU) 2016/679). The DPDs will ensure, in an independent manner, the internal application of the provisions of the Regulation in their institutions and will keep a register of all the processing operations including personal data in PICCOLO. The Register, which must contain information explaining the purpose and conditions of the processing operations, should be accessible to any interested person.

Moreover, an evaluation of the data risk assessment has been preformed concluding there is no need to add another layer of anonymization to data in order to make it open accessible. (See Annex 6). Although an impact assessment including this report should be performed and evaluated by the Basque Country Ethics Committee at the end of the project.

6.1.2 Is informed consent for data sharing and long term preservation included in questionnaires dealing with personal data?

Ethical approvals for the PICCOLO project were obtained from the relevant Ethics Committees at the early stage of the project, as included in D7.1. However, at this phase of the project other updates/approvals have been received:

a) BIOEF: Approval from the Basque Ethics Committee related to the re-use of the histological images (base on colon disease) acquired during BIOPOOL project (see annex 1) and modification of the clinical data associated to the human samples (see annex 2). In this sense, a new clinical text datasheet focused on the description of the video, including endoscopic and pathologic diagnosis was approved by the competent ethics committee (see annex 6).
b) Imperial College Healthcare Tissue Bank received a renewal of ethical approval (see annex 3).

Informed consents (were all approved by the competent Ethical Committees and as mentioned in D7.1, D7.4, D10.1 and D10.2) will be used in both institutions (Imperial College and BIOEF) for image and video acquisition and data collection. Only data from patients able to give informed consent will be included in the study.

7. Other

7.1.1 Do you make use of other national/funder/sectorial/departmental procedures for data management? If yes, which ones?

Since institutions from different countries (UK and Spain) will generate data in the PICCOLO project, each country will carry out their research according to their Data Protection Law. The following documents will be used as reference:

- Royal Decree 1720/2007, of 21 December, which approves the Regulation implementing Organic Law 15/1999, of 13 December, on the Protection of Personal Data (Spanish Data Protection Agency).
- European Data Protection Directive.
- The Data Protection Act, 1998 (UK).

Note: Refer to Article 29 of the Grant Agreement of the PICCOLO project for **DISSEMINATION OF RESULTS — OPEN ACCESS — VISIBILITY OF EU FUNDING.**

8. Conclusions/Further work

This document delivered at M31 contains all necessary ethical aspects related to the use of health data during the project that could be fulfilled at this stage.

The DMP has been elaborated based on the Guideline on FAIR Data Management in Horizon 2020 described in D7.1 and it is intended to be a living document in which information can be made available on a finer level of granularity through updates as the implementation of the project progresses and when significant changes occur.

At this time, DMP includes possible scenarios for making data openly available, that would be carried out at the end of the project.

Moreover, updates of the ethical approvals have been included as annexes (see 6.1.2).

References

[1] PICCOLO H2020 Project, Multimodal highly-sensitive PhotonICs endoscope for improved in-vivo COLOn Cancer diagnosis and clinical decision support. 2017-2020. Available at: www.piccolo-project.eu

Disclaimer

This deliverable has been prepared in the context of the funded project PICCOLO. This project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 732111.

This deliverable reflects only the author's views and the Commission is not responsible for any use that may be made of the information contained therein.

Annex 1

Ethical Approval to use BIOPOOL database (BIOEF)

Issued by: Euskadi Clinical Research Ethics Committee

CEIm
Euskadiko Medikamentuen gaineko Ikerkuntza Batzorde Etikoa
Comité de Ética de Investigación con medicamentos de Euskadi

EUSKO JAURLARITZA
GOBIERNO VASCO
OSASUN SAILA
DEPARTAMENTO DE SALUD

Arantza Hernández Gil
Secretaria del CEIm Comunidad Autónoma del País Vasco (CEIm-E)

CERTIFICA

1- Que el CEIm Comunidad Autónoma del País Vasco (CEIm-E) en su reunión del día 25/10/2017, acta 10/2017 ha evaluado la solicitud de cesión del biobanco en relación a la cesión de Imágenes Histológicas para el proyecto:

Título: **Título: Multimodal highly-sensitive photonics endoscope for improved in-vivo colon cáncer diagnosis and clinical decision support - PICCOLO**
IP: Artzai Picón (Tecnalia)
Cesión de imágenes histológicas (no muestras físicas)

Código Promotor: **17-14** Código Interno: CES-BIOEF 2017-16

2- Considera que

- La cesión se ha planteado siguiendo los requisitos de la Ley 14/2007, de 3 de julio, de Investigación Biomédica y el Real Decreto 1716/2011, de 18 de noviembre, por el que se establecen los requisitos básicos de autorización y funcionamiento de los biobancos con fines de investigación biomédica y del tratamiento de las muestras biológicas de origen humano, y se regula el funcionamiento y organización del Registro Nacional de Biobancos para investigación biomédica.
- Se cumplen los requisitos necesarios para la gestión de muestras.

3- Se acuerda emitir informe favorable a la solicitud de cesión de imágenes histológicas. Se recuerda que cuando se disponga de más información se debe enviar un informe con los resultados incluso publicaciones, si las hubiere.

Por lo que este CEIm, actuando como comité externo al Biobanco, y reunido el 25/10/2017 (recogido en acta 10/2017) emite el correspondiente DICTAMEN FAVORABLE

Lo que firmo en Vitoria, a 10 de noviembre de 2017

Fdo:

ARANTZAZU HERNANDEZ GIL

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Nombre de reconocimiento (DN): c=ES, o=Eusko Jaurlaritza, ou=SALUD, ou=Ziurtagiri onartua - Certificado reconocido, ou=Entitate publikoen ziurtagiri - Certificado de entidad publica, ou=Condiciones de uso en www.izenpe.com nola erabili jakiteko, dnQualifier=-dni 44678219Y -cif S4833001C, cn=ARANTZAZU HERNANDEZ GIL, givenName=ARANTZAZU, sn=HERNANDEZ, serialNumber=44678219Y
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Arantza Hernández Gil
Secretaria del CEIm Comunidad Autónoma del País Vasco (CEIm-E)

Annex 2

Amendment Ethical Approval (BIOEF), November 2017

Issued by: Euskadi Clinical Research Ethics Committee

CEIm
Euskadiko Medikamentuen gaineko Ikerkuntza Batzorde Etikoa
Comité de Ética de Investigación con medicamentos de Euskadi

EUSKO JAURLARITZA
GOBIERNO VASCO
OSASUN SAILA
DEPARTAMENTO DE SALUD

INFORME DEL COMITE ETICO DE INVESTIGACION CLINICA DE EUSKADI (CEIC-E)

Arantza Hernández Gil
Secretaria del CEIC Comunidad Autónoma del País Vasco (CEIC-E)

CERTIFICA

Que este Comité de acuerdo a la ley 14/2007 de Investigación Biomédica, principios éticos de la declaración de Helsinki, el Real Decreto 1716/2011, de 18 de noviembre, por el que se establecen los requisitos básicos de autorización y funcionamiento de los biobancos con fines de investigación biomédica y del tratamiento de las muestras biológicas de origen humano, y se regula el funcionamiento y organización del Registro Nacional de Biobancos para investigación biomédica y resto de principios éticos aplicables, en su reunión del día 25/10/2017, acta 10/2017, ha evaluado la propuesta del promotor para que se realice la modificación del cuaderno de recogida de datos y documento explicativo a los donantes de la solicitud con código 17-14:

Título: Multimodal highly-sensitive photonics endoscope for improved in-vivo colon cáncer diagnosis and clinical decision support – PICCOLO
IP: Artzai Picón (Tecnalia) en el estudio:

Título: Multimodal highly-sensitive photonics endoscope for improved in-vivo colon cáncer diagnosis and clinical decision support - PICCOLO

Código Promotor: 17-14 Código Interno: PI+CES BIOEF 2017-03

Versión Hoja Información al Paciente evaluada: GENERAL / V3, 30/08/17
Versión Cuaderno de Recogida de datos evaluada: V2, 30/08/17

Y que este Comité ha decidido emitir INFORME FAVORABLE A LA REALIZACIÓN DE DICHA ENMIENDA.

Lo que firmo en Vitoria, a 07 de noviembre de 2017

ARANTZAZU HERNANDEZ GIL

Firmado digitalmente por ARANTZAZU HERNANDEZ GIL
Nombre de reconocimiento (DN): c=ES, o=Eusko Jaurlaritza, ou=SALUD, ou=Ziurtagiri onartua - Certificado reconocido, ou=Entitate publikoen ziurtagiri - Certificado de entidad publica, ou=Condiciones de uso en www.izenpe.com nola erabili jakiteko, dnQualifier=-dni 44678219Y -cif S4833001C, cn=ARANTZAZU HERNANDEZ GIL, givenName=ARANTZAZU, sn=HERNANDEZ, serialNumber=44678219Y
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Arantza Hernández Gil
Secretaria del CEIC Comunidad Autónoma del País Vasco (CEIC-E)

Nota: Una vez comenzado el estudio, se recuerda la obligación de enviar un **informe de seguimiento anual** e **informe final** que incluya los resultados del estudio (si el estudio dura menos de un año, con el informe final será suficiente). Más información en la página web del CEIC-E:
http://www.osakidetza.euskadi.eus/informacion/proyectos-de-investigacion/r85-pkfarm03/es/

Annex 3

Imperial College's Tissue Bank Ethical Approval (renewal, July 2017)

Issued by: Research Ethics Committee (REC) for Wales

Ymchwil Iechyd a Gofal Cymru
Health and Care Research Wales

Gwasanaeth Moeseg Ymchwil
Research Ethics Service

Ariennir gan **Lywodraeth Cymru**
Funded by **Welsh Government**

Wales REC 3
Health and Care Research Support Centre
Castlebridge 4
15-19 Cowbridge Road East
Cardiff CF11 9AB

Telephone : 029 2078 5741
E-mail : helen.williams19@wales.nhs.uk
Website : www.hra.nhs.uk

25 July 2017

Professor Geraldine A Thomas
Imperial College Healthcare Tissue Bank
Room 11L04
Charing Cross Hospital
Fulham Palace Road, London
W6 8RF

Dear Professor Thomas

Title of the Research Tissue Bank:	**Imperial College Healthcare Tissue Bank**
REC reference:	**17/WA/0161**
Designated Individual:	**Professor Geraldine A Thomas**
IRAS project ID:	**229026**

Thank you for your letter of 11 July 2017, responding to the Committee's request for further information on the above research tissue bank and submitting revised documentation.

The further information has been considered on behalf of the Committee by the Vice-Chair.

We plan to publish your research summary wording for the Research Tissue Bank on the HRA website, together with your contact details. Publication will be no earlier than three months from the date of this favourable opinion letter. The expectation is that this information will be published for all Research Tissue Banks that receive an ethical opinion but should you wish to provide a substitute contact point, wish to make a request to defer, or require further information, please contact hra.studyregistration@nhs.net outlining the reasons for your request. Under very limited circumstances (e.g. for student research which has received an unfavourable opinion), it may be possible to grant an exemption to the publication of the Research Tissue Bank.

Confirmation of ethical opinion
On behalf of the Committee, I am pleased to confirm a favourable ethical opinion of the above research tissue bank on the basis described in the application form and supporting documentation as revised.

The Committee has also confirmed that the favourable ethical opinion applies to all research projects conducted in the UK using tissue or data supplied by the tissue bank, provided that the release of tissue or data complies with the attached conditions. It will not be necessary for these researchers to make project-based applications for ethical approval. They will be deemed to have ethical approval from this committee. You should provide the researcher with a copy of this letter as confirmation of this. The Committee should be notified of all projects receiving tissue and data from this tissue bank by means of an annual report.

This application was for the renewal of a Research Tissue Bank application. The previous REC Reference number for this application was 12/WA/0196.

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Duration of ethical opinion
The favourable opinion is given for a period of five years from the date of this letter and provided that you comply with the standard conditions of ethical approval for Research Tissue Banks set out in the attached document. You are advised to study the conditions carefully. The opinion may be renewed for a further period of up to five years on receipt of a fresh application. It is suggested that the fresh application is made 3-6 months before the 5 years expires, to ensure continuous approval for the research tissue bank.

Research Tissue Bank Renewals
The Research Tissue Bank has been renewed for a further five years from the end of the previous five year period. The previous five year period ran from 17 July 2012 to 17 July 2017. This Research Tissue Bank may be renewed for further periods of five years at a time by following the process described in the above paragraph.

Approved documents
The documents reviewed and approved at the meeting were:

Document	Version	Date
Covering letter on headed paper [Cover note]	1	12 May 2017
Covering letter on headed paper [Cover note]		11 July 2017
Human Tissue Authority licence [HTA Licence]	1	22 March 2010
IRAS Checklist XML [Checklist_12052017]		12 May 2017
IRAS Checklist XML [Checklist_15052017]		15 May 2017
IRAS Checklist XML [Checklist_18052017]		18 May 2017
IRAS Checklist XML [Checklist_11072017]		11 July 2017
Other [Annex 2]	1	03 May 2017
Other [Annex 4]	1	26 April 2017
Other [Annex 1]	1	12 May 2017
Other [Annex 10]	1	10 May 2017
Other [Annex 11]	2	10 May 2017
Other [G Thomas CV]	1	12 May 2017
Other [Annex 5]	v2	10 May 2017
Other [Annex 7]	v2	10 May 2017
Other [Annex 6]	v1.1	11 July 2017
Other [Annex 8]	1.1	20 June 2017
Other [Annex 9]	1.1	11 July 2017
Other [PIS xenografting track change]	v2	10 July 2017
Other [PIS T&GCT]	1.1	20 June 2017
Other [RIS T&GCT]	1.1	20 June 2017
Other [Health Volunteer TB-DOC-PI3]	3.1	20 June 2017
Other [Provisional opinion letter]		12 June 2017
Participant consent form [Discover PIS v1.1 track change]	1.1	11 July 2017
Participant information sheet (PIS) [Annex 3]	v1.1	11 July 2017
Protocol for management of the tissue bank [Project description]	1	12 May 2017
REC Application Form [RTB_Form_15052017]		15 May 2017
REC Application Form [RTB_Form_11072017]		11 July 2017

Thank you for providing a copy of the above licence.

Research governance
Under the Research Governance Framework (RGF), there is no requirement for NHS research permission for the establishment of research tissue banks in the NHS. Applications to NHS R&D offices through IRAS are not required as all NHS organisations are expected to have included management review in the process of establishing the research tissue bank.

Research permission is also not required by collaborators at tissue collection centres (TCCs) who provide tissue or data under the terms of a supply agreement between the organisation and the research tissue bank. TCCs are not research sites for the purposes of the RGF.

Research tissue bank managers are advised to provide R&D offices at all TCCs with a copy of the REC application for information, together with a copy of the favourable opinion letter when available. All TCCs should be listed in Part C of the REC application.

NHS researchers undertaking specific research projects using tissue or data supplied by a research tissue bank must apply for permission to R&D offices at all organisations where the research is conducted, whether or not the research tissue bank has ethical approval.

Site-specific assessment (SSA) is not a requirement for ethical review of research tissue banks.

Registration of Research Tissue Banks
It is a condition of the ethical approval that all Research Tissue Banks are registered on the UK Clinical Research Collaboration (UKCRC) Tissue Directory. The Research Tissue Bank should be registered no later than 6 weeks after the date of this favourable ethical opinion letter or 6 weeks after the Research Tissue Bank holds tissue with the intention to provide for research purposes. Please use the following link to register the Research Tissue Bank on the UKCRC Directory: https://directory.biobankinguk.org/Register/Biobank Registration is defined as having added details of the types of tissue samples held in the tissue bank.

There is no requirement to separately notify the REC but you should do so at the earliest opportunity e.g. when submitting an amendment or annual progress report form. We will monitor the registration details as part of the annual progress reporting process.

Statement of compliance
The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

After ethical review
Reporting requirements

The attached standard conditions give detailed guidance on reporting requirements for research tissue banks with a favourable opinion, including:

- Notifying substantial amendments
- Submitting Annual Progress reports

The HRA website also provides guidance on these topics, which is updated in the light of changes in reporting requirements or procedures.

User Feedback
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17/WA/0161	Please quote this number on all correspondence

Yours sincerely

Mrs Helen Williams
Health and Care Research Wales
Research Ethics Committee Co-ordinator

Email - helen.williams19@wales.nhs.uk

pp **Mrs Monika Hare**
Vice Chair

Enclosures: Standard approval conditions

Copy to: Professor Geraldine A Thomas, Imperial College London

Annex 4

Informed Consent for wide-field colonoscopy videos (BIOEF)

MODELO DE HOJA DE INFORMACIÓN AL PACIENTE PARA PROYECTOS DE INVESTIGACIÓN QUE IMPLIQUEN LA UTILIZACIÓN DE MUESTRAS BIOLÓGICAS

Versión del modelo aprobado por el CEIC-E 30 de Abril de 2014

TÍTULO DEL PROYECTO: Multimodal highly-sensitive photonics endoscope for improved in-vivo colon cáncer diagnosis and clinical decision support - PICCOLO

INVESTIGADOR PRINCIPAL: Artzai Picón de Tecnalia

ENTIDAD FINANCIADORA: HORIZON 2020

DESCRIPCIÓN GENERAL:

Considerando que usted o su familiar está participando en el Programa de Cribado del cáncer de colon, le solicitamos su consentimiento para participar en un estudio del que le informamos a continuación. Antes de decidir si quiere participar o no, le rogamos lea detenidamente este documento que incluye la información sobre este proyecto. Puede formular todas las preguntas que le surjan y solicitar cualquier aclaración sobre cualquier aspecto del mismo

PROPÓSITO DEL ESTUDIO: Tal y como ha leído en la hoja informativa que le han proporcionado anteriormente, el el proyecto PICCOLO pretende desarrollar un nuevo endoscopio que incorpore mejoras con respecto a los actuales con objeto de ayudar a los médicos a hacer un diagnóstico más rápido.

EXPLICACIÓN DEL ESTUDIO: Si usted accede a participar en este estudio, será necesario que acepte que se pueda utilizar el vídeo de su colonoscopia para el desarrollo de este nuevo endoscopio.
No hay contraprestación económica de ningún tipo.

DATOS A RECOGER: Como parte de este proyecto aprobado por el Comité Ético de Investigación Clínica de Euskadi se le va a solicitar autorización para utilizar el VIDEO de su colonoscopia con fines de investigación, con objeto de aumentar los conocimientos sobre el aparato objeto de estudio.

La realización de la prueba diagnóstica de la colonoscopia corresponde a la práctica clínica.

El vídeo de la colonoscopia será estudiado por los socios del proyecto PICCOLO.

BENEFICIO Y ATENCIÓN MÉDICA: No recibirá ningún beneficio por su participación en este estudio.
Su participación en este estudio es completamente voluntaria: Si usted decide no participar recibirá todos los cuidados médicos que pudiera necesitar y su relación con el equipo médico que le atiende no se verá afectada.

TRATAMIENTO DEL VIDEO Y CONFIDENCIALIDAD. Se solicita su consentimiento para la utilización del vídeo de su colonoscopia para el desarrollo de este proyecto. El vídeo se recogerá empleando un procedimiento de anonimización. Nadie podrá relacionar el vídeo con Vd.

La información será procesada durante el análisis de los resultados obtenidos y aparecerá en los informes finales. En ningún caso será posible identificarle, garantizándole la confidencialidad de la información obtenida, en cumplimiento de la legislación vigente.

DESTINO DEL VIDEO TRAS SU UTILIZACIÓN EN ESTE PROYECTO DE INVESTIGACIÓN

Una vez finalizada la investigación, se le ofrecen las siguientes opciones:

A. La **destrucción** del vídeo.

B. Su **utilización en futuros proyectos** de investigación biomédica relacionados con el APARATO DIGESTIO, o para cualquier fin de investigación (preferentemente relacionados con el APARATO DIGESTIVO). A tal fin, se le ofrece la opción de donar el vídeo al **Biobanco Vasco** de la Fundación Vasca de Innovación e Investigación Sanitaria (BIOEF) con objeto de que pueda ser conservado y destinado a futuras investigaciones. En este caso, firmará el consentimiento específico incluido en este documento, que será custodiado por el coordinador del BIOBANCO de su Hospital.

ALMACENAMIENTO DEL VIDEO EN EL BIOBANCO. Con la firma del consentimiento anexo, Vd. autoriza al Biobanco Vasco, al almacenamiento y utilización de su vídeo, para la realización de proyectos de investigación que cumplan con los principios éticos y legales aplicables.

El clínico responsable de la investigación entregará al Biobanco los datos clínicos asociados, y el vídeo, conforme a su voluntad, para su almacenamiento en las instalaciones del centro hospitalario adscritas al Biobanco, así como el documento de consentimiento informado por usted firmado. En el hospital Universitario Basurto se registrarán los datos que pudieran relacionarle con las muestras a conservar, empleando un procedimiento de anonimización. NADIE podrá relacionar estos datos con Vd.

La donación de muestras/vídeo para investigación es voluntaria y altruista. Su único beneficio es el que corresponde al avance de la medicina en beneficio de la sociedad. Su vídeo no podrá ser objeto directo de actividades con ánimo de lucro. No obstante, la información generada a partir de los estudios realizados sobre el vídeo podría ser fuente de beneficios comerciales. En tal caso, se pretende que estos beneficios reviertan en la salud de la población, aunque no de forma individual ni en el donante ni en sus familiares.

Los resultados de futuros estudios podrán ser comunicados en reuniones científicas, congresos médicos o publicaciones científicas. Siempre se mantendrá una estricta confidencialidad sobre su identidad.

La donación de su vídeo no supone ningún gasto extra.

ANEXO ACLARATORIO

SE GARANTIZA QUE LA REALIZACIÓN DE ESTE PROYECTO, EL TRATAMIENTO, ALMACENAMIENTO Y UTILIZACIÓN DEL VIDEO ALMACENADO EN EL BIOBANCO CUMPLIRÁ CON LA **NORMATIVA APLICABLE**:

Ley Orgánica 15/1999, de 13 de diciembre, de Protección de Datos de Carácter Personal. En observancia a esta ley los datos de carácter personal recogidos en este estudio pasarán a formar parte de un fichero automatizado que reúne las medidas de seguridad de nivel alto.

Ley 41/2002, de 14 de noviembre, básica reguladora de la autonomía del paciente y de derechos y obligaciones en materia de información y documentación clínica

Ley 14/2007, de 3 de julio, de Investigación biomédica.

Real Decreto 1716/2011, de 18 de noviembre, por el que se establecen los requisitos básicos de autorización y funcionamiento de los biobancos con fines de investigación biomédica y del tratamiento de las muestras biológicas de origen humano, y se regula el funcionamiento y organización del Registro Nacional de Biobancos para investigación biomédica

¿QUÉ ES UN BIOBANCO?

Un **biobanco** es un centro de conservación, en condiciones adecuadas, de muestras, tejidos, ADN y otros derivados, representan un valioso instrumento con destino a la investigación de enfermedades y que puede permitir la obtención de conocimientos que sirvan para el desarrollo de nuevas estrategias y terapias aplicables a pacientes.

El Biobanco de BIOEF está constituido en nodos, uno de los cuales está ubicado en el Hospital Universitario Basurto, en donde se almacenará y conservará su vídeo.

Los proyectos de investigación realizados con el vídeo almacenado en el Biobanco serán aprobados por un Comité de Ética de la Investigación, y, si procede, autorizado por la autoridad sanitaria pertinente, previo informe favorable de los comités ético y científico externos del biobanco.

Tanto el Biobanco Vasco, como el investigador al que en un futuro se pueda ceder el vídeo, son responsables del manejo de los Datos, conforme a la Ley orgánica 15/1999, de 13 de diciembre, sobre Protección de Datos de Carácter Personal. El Hospital Universitario Basruto garantiza que en ningún caso saldrá del centro dato alguno que le identifique personalmente.

CONSENTIMIENTO PARA LA REALIZACIÓN DEL PROYECTO DE INVESTIGACIÓN

Investigador/Responsable clínico: Dr. Francisco Polo

TÍTULO DEL PROYECTO: Multimodal highly-sensitive photonics endoscope for improved in-vivo colon cáncer diagnosis and clinical decision support - PICCOLO

Yo……con DNI…..... declaro que he leído la Hoja de Información al paciente, de la que se me ha entregado una copia. He recibido información sobre las características del estudio, así como los posibles beneficios y riesgos que puedo esperar, los derechos que puedo ejercitar, y las previsiones sobre el tratamiento de datos y muestras. He recibido suficiente información sobre el estudio.

Sé que se mantendrá en secreto mi identidad y que mi video será anonimizado.

Yo doy mi consentimiento para que se utilicen mi vídeo y los datos clínicos asociados como parte de **este proyecto de investigación**. Consiento en participar voluntariamente.

Afirmo haber sido advertido sobre las opciones de destino del vídeo al finalizar el proyecto de investigación.

En este sentido: Solicito la destrucción del vídeo □

Solicito la incorporación del vídeo en el Biobanco Vasco □

Fecha …… Firma del paciente ……..

Fecha …….. Firma representante legal (si procede)……..

Nombre representante legal:

Relación con el paciente:

Constato que he explicado las características del proyecto de investigación y las condiciones de conservación, si procede, que se aplicarán al vídeo y a los datos conservados.

Nombre del Investigador o la persona designada para proporcionar la información:

Fecha …… Firma ……

CONSENTIMIENTO PARA LA DONACIÓN DEL VÍDEO AL BIOBANCO VASCO

Responsable clínico: Dr. Francisco Polo

Yo_____

He sido informado sobre la posibilidad de transferir y almacenar el vídeo junto con la información clínica relacionada al Biobanco Vasco de forma anonimizada.

He sido informado sobre la finalidad de la **conservación,** el lugar de conservación, así como sobre las garantías de cumplimiento de la legalidad vigente y de la posibilidad de ceder el vídeo para futuros proyectos de investigación. Se me ha informado que el presente consentimiento será custodiado en las instalaciones del Nodo del Biobanco en el Hospital Universitario Basurto.

Yo **DOY** mi consentimiento para que el Hospital Universitario Basurto transfiera mi vídeo y los datos de salud relevantes (excepto los que me identifiquen) del AREA DEL APARATO DIGESTIVO, al Biobanco Vasco.

Doy mi consentimiento para que:

- ☐ el vídeo se utilice sólo para **proyectos relacionados con EL APARATO DIGESTIVO**
- ☐ el vídeo se utilice para **cualquier investigación biomédica** (preferentemente relacionado con el área del aparato digestivo)

Fecha …… Firma del paciente ……

Fecha :…….. Firma representante legal (si procede)……..

Nombre representante legal:

Relación con el paciente:

Constato que he explicado las características de las condiciones de conservación y seguridad que se aplicarán al vídeo y a los datos clínicos conservados.

Nombre del clínico responsable

Fecha …… Firma ……

Annex 5

Risk Assessment Report

Performed by Global Factory

Basque Foundation for Health Innovation and Research (BIOEF) -

Piccolo Project

Risk analysis_v01

CONTENTS

1. INTRODUCTION

In Article 35 of 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 (the General Data Protection Regulation, hereon GDPR), it is established that a data protection impact assessment (DPIA) will be carried out concerning privacy when data processing is "likely to result in a high risk to the rights and freedoms of individuals".

The GDPR does not formally define the concept of a DPIA as such, but its minimal content is specified by Article 35(7) as follows:

- *"(a) a systematic description of the envisaged processing operations and the purposes of the processing, including, where applicable, the legitimate interest pursued by the controller;*
- *(b) an assessment of the necessity and proportionality of the processing operations in relation to the purposes;*
- *(c) an assessment of the risks to the rights and freedoms of data subjects referred to in paragraph 1; and*
- *(d) the measures envisaged to address the risks, including safeguards, security measures and mechanisms to ensure the protection of personal data and to demonstrate compliance with this Regulation taking into account the rights and legitimate interests of data subjects and other persons concerned";*

- its meaning and role are clarified by Recital 84 as follows:

> *"In order to enhance compliance with this Regulation where processing operations are likely to result in a high risk to the rights and freedoms of natural persons, the controller should be responsible for the carrying-out of a data protection impact assessment to evaluate, in particular, the origin, nature, particularity and severity of that risk."*

In line with the risk-based focus of the GDPR, it is not mandatory to conduct a DPIA for all processing operations. Rather, such an assessment is only required when the processing is likely to "result in a high risk to the rights and freedoms of individuals"

It is therefore necessary to determine in what circumstances an impact assessment must be conducted and, if so, how to determine how it should be conducted in view of the fact that a processing operation involves a high risk.

In relation to this, the Spanish Data Protection Agency (AEPD) has issued guidance documents on compliance with European regulations for public bodies, in particular, a document entitled "THE IMPACT OF THE GENERAL DATA PROTECTION REGULATION ON THE ACTIVITY OF PUBLIC BODIES". The agency establishes the need for public bodies to assess

> *"[…] whether the processing they undertake requires a DPIA because it carries a high risk to the rights and freedoms of individuals involved and have available a method for conducting such an assessment. The GDPR establishes that processing operations that are likely to result in a high risk to the rights and freedoms of individuals involved should be subject to a DPIA before they commence. The GDPR identifies some cases in which it is assumed that there is a high risk and envisages that national data protection authorities will publish lists of other high-risk processing operations. It also outlines the minimal content of impact assessments."*

How can it be determined whether a processing operation results in a high risk to the rights and freedoms of individuals?

In the aforementioned document, the agency explains the need to conduct risk analysis in the following way:

> *"The need to conduct an analysis of the risk to the rights and freedoms of individuals for all data processing operations undertaken. The GDPR makes the application of all foreseen compliance measures by controllers and processors dependent on the level and type of risk implied by each processing operation for the rights and freedoms of individuals involved. To this end, all processing, both ongoing and that expected to be initiated, should be subject to a risk analysis. In the context of public bodies, risk analysis methods are available, mainly focusing on information security. These methods should be widened to include risks associated with failure to comply with the GDPR."*

In the context of public bodies, although methods and tools focused on risk analysis and management are certainly available, they may not be suited to the case of the processing of personal data. Therefore, while inspection agencies consider that risk analysis should be conducted for all processing that is ongoing or expected to be initiated, the risk analysis methods should also be adapted to the type of item to be checked, such as personal data, considering whether their management may affect fundamental rights and freedoms.

In line with this, if the general rule establishes that a “risk” is a scenario encompassing an event and its consequences, estimated in terms of severity and likelihood, in this document, processing operations are analysed by application of a questionnaire developed based on the obligations set out in the data protection legislation.

Similarly, “risk management” is defined as the coordinated activities to direct and control an organization with regard to risk. In relation to this, in accordance with the GDPR, the assessment and management of high risks that might have an impact on rights and freedoms of individuals fit with the DPIA provided for in the legislation.

2. OBJECTIVE AND SCOPE OF THE ANALYSIS

2.1. OBJECTIVE

BIOEF commissions the consultant to conduct a risk analysis with a view to applying the current data protection legislation to a data set that is to be processed as part of a research project.

Specifically, BIOEF is currently involved in a European data analysis project called PICCOLO in collaboration with other institutions and organizations. The objective of the project is to gather anonymous information from images obtained by innovative endoscopic techniques helping provide gastroenterologists with immediate and detailed in situ identification of neoplastic lesions.

This European project in which BIOEF is involved will be undertaken in the following order: first, BIOEF will receive anonymized data from the source, namely, the Basque Health Service (Osakidetza[1]) (with prior informed consent of the patient), obtained using the project's own image capture system, for the purpose of storing them in a data repository for the project, and then analysing, studying and classifying them in accordance with the goals of the project.

In this scenario, BIOEF needs a risk analysis to be undertaken in relation to the data it will receive from Osakidetza to determine whether processing of the personal data is possible and, accordingly, whether the anonymization at source by Osakidetza has been performed adequately or, on the other hand, the analysis detects risk situations that need to be managed and vulnerabilities for the organization and, by extension, for the project that need to be mitigated.

2.2. SCOPE OF THE ANALYSIS

In line with the objective of the data analysis project outlined in the previous section, in this report, Global Factory presents a risk analysis of the data to be sent from Osakidetza to BIOEF, seeking to check whether the anonymization has been performed adequately in compliance with current data protection legislation.

[1] Osakidetza, name for the Basque Health Service in the Basque language, used hereon.

BIOEF has supplied documentation in Excel listing the specific types of data that will be received from Osakidetza, namely:

PICCOLO: HUMAN METADATA (videos)

- **CODE**
- **NUMBER OF POLYPS OF INTEREST (N)**
- **CURRENT POLYP ID (X/N)**
- **POLYP SIZE (mm)**
- **PARIS CLASSIFICATION**
- **NICE CLASSIFICATION (NBI Vascular pattern)**
- **PRELIMINARY DIAGNOSIS**
- **LITERAL DIAGNOSIS**
- **HISTOLOGICAL STRATIFICATION**
- **ADDITIONAL FINDINGS**

And at a later stage,

PICCOLO: HUMAN METADATA (images)

- **CODE**
- **AGE**
- **SEX**
- **REASON FOR COLONOSCOPY**
- **COLONOSCOPY DATE_TIME**
- **NUMBER OF POLYPS FOUND (N)**
- **CURRENT POLYP ID (X/N)**
- **POLYP SIZE (mm)**
- **POLYP LOCALIZATION**
- **KUDO´S PIT PATTERN**
- **PARIS CLASSIFICATION**
- **NICE CLASSIFICATION (NBI Vascular pattern)**
- **BOSTON BOWEL PREPARATION SCALE**
- **MORPHOLOGIC DIAGNOSIS (SNOMED Code)**
- **TOPOGRAPHIC DIAGNOSIS (SNOMED Code)**
- **PRELIMINARY DIAGNOSIS**
- **LITERAL DIAGNOSIS**
- **HISTOLOGICAL STRATIFICATION**
- **PREVIOUS TREATMENT**
- **RECURRENCE**
- **ADDITIONAL FINDINGS**

This information to be sent by Osakidetza will be submitted to a risk analysis considering the provisions of the data protection legislation and crucially the guidance issued by the Spanish

Data Protection Agency concerning the anonymization of data that should be carried out in the context of health research projects.[2]

[2] *Orientaciones y garantías en los procedimientos de anonimización de datos personales.* [Guidelines and safeguards in personal data anonymization procedures] *Spanish Data Protection Agency (2016).*

2.3. WORKING GROUP

In accordance with the needs of the organization that has commissioned this service, a risk analysis is to be performed, and hence, participation is required from individuals holding the following positions in each participating organization:

POSITION	ORGANIZATION	ACTIONS
Director	BIOEF	Assessment and supervision of the project
Coordinator of Projects	BIOEF	Analysis of documents
Legal Director	Global Factory	Performance of interviews Development of working method Presentation of the results
Legal advisor on technology law	Global Factory	Analysis of documents Analysis of risks Drafting of the report

No participation of third parties, other companies or organizations participating in the PICCOLO project, is required for either the preparation or the analysis of this document.

3. METHODS

3.1. WORKING METHOD

In the context of risk analysis for research projects, interviews need to be carried out to serve as a basis for determining the scope of the report to be submitted.

Further, BIOEF has provided documents that will be analysed and assessed by Global Factory.

3.2. RISK ANALYSIS METHOD

In the context of data protection, the main type of item on which the analysis will centre is data of a personal nature.

Using a series of questions concerning compliance with the legislation, it is possible to detect the vulnerabilities of the organization in relation to the processing of personal data, and hence, the information which needs to be properly managed to avoid negative consequences for the organization (loss of information, loss of reputation, costs, fines, etc.).

The issues identified, that will later be confirmed through risk analysis, offer a real view of the possibility that something may occur that will have an impact on and consequences for the management of data by the organization, and hence, the fundamental rights and freedoms of individuals.

The risk is calculated by multiplying the estimated likelihood of an event occurring by the severity of impact it could have for the organization.

Specifically, in the present case, the likelihood is rated from 1 to 5, where 1 corresponds to a very low and 5 a very high probability.

The severity of impact is also rated numerically, in this case, from 1 to 3, where 1 corresponds to a low severity, that is, a low level of impact, and 3 to the highest possible severity, that is, a very high level of impact on the organization.

In this way, considering the likelihood of the risk times its severity, we obtain a total assessed risk, as set out in the following table:

			Severity		
			Low 1	Moderate 2	High 3
Likelihood	Very High	5	5	10	15
	High	4	4	8	12
	Moderate	3	3	6	9
	Low	2	2	4	6
	Very Low	1	1	2	3
	Very severe risk: urgent preventive measures required; data processing should not be started without applying such measures and safeguards and without substantially limiting the risk.				
	Major risk: mandatory to apply preventive measures; risk factors should be monitored prior to or during data processing.				
	Appreciable risk: assess whether preventive measures can be introduced to reduce the level of risk; if this were not to be possible, risk factors should be monitored.				
	Marginal risk: Risk should be monitored but no preventive measures are needed at the outset.				

According to the types of risks defined, the level of risk can be obtained for each item to be controlled, and overall, for each type of risk analysed.

Once the level of risk has been determined for each area subject to control, conclusions can be drawn concerning the extent of the total plausible risk for the organization in a specific area monitored, that is, whether there are very severe, major, appreciable or only marginal risks.

The result of the analysis has to be subjected to close examination and evaluated by the organization given that, in the event that it is found that the data processing could pose a high risk, then the risk would need to be managed, this meaning that, under current data protection legislation, there would be a need to conduct a DPIA, as that would be the suitable approach for managing the risk.

4. RISK ANALYSIS

4.1. LEGAL FRAMEWORK APPLICABLE TO THE CIRCUMSTANCES

DATA PROTECTION LAW

Article 3 of the definitions of Organic Law 15/1999 on the protection of personal data makes provisions for anonymization:

> *"f) Anonymization procedure: all processing of personal data such that the information obtained cannot be attributed to an identified or identifiable person."*

Anonymization of personal data produces an effect that is completely irreversible such that it is not possible to revert it or track back. Therefore, it is not possible to know the personal data that were originally processed.

> *"Article 11*
>
> *[…]*
>
> *6. If the transfer occurs prior to anonymization, the provisions established in the previous sections do not apply."*

In line with the aforementioned definition, it is not possible to apply the rules and conditions of data protection applicable to data transfer if the data have already been anonymized. This would be the case if, for example, we only transfer first names of individuals (without any additional information, such as their identity number, surnames, etc. that could make them identifiable) or statistics such as the number of people in a given age range, or similar figures.

Concerning definitions, Article 5.1 of the Royal Decree 1720/2007 on the development of the Organic Law on data protection stipulates the following in Sections e and p:

> *"[…]*
>
> *e) Anonymized data: data which do not allow identification of the person to whom they relate*
>
> *p) Anonymization procedure: Processing of personal data whereby we obtain irreversibly de-identified data."*

Therefore, once an anonymization procedure has been applied to personal data, there are no means by which the resulting information can be used to identify any individual. That is, there is no reverse process by which it is possible to recover the original data.

HEALTHCARE LAW

Law 41/2002, of 14 November, regulating patient autonomy and their rights and obligations in relation to clinical information and documentation uses the concept of anonymous data in its Article 16 on the use of medical records.

> *"Article 16. Uses of health records.*
>
> *1. […]*
>
> *2. […]*
>
> *3. Access to medical records for judicial, epidemiological, public health, research or teaching purposes is governed by Organic Law 15/1999, of 13 December, on the protection of personal data, and Law 14/1986, of 25 April, General Health Act, and other legislation applicable in each case. Access to medical records for these purposes makes it necessary to store personal identifying data for the individual patient separately from those of clinical and healthcare nature, such that, as a general rule, **anonymity** continues to be safeguarded, except when patients themselves have consented to them not being separated."*

Article 16(3) stipulates that, to ensure the safety and anonymity of patients, identifying data are separated from strictly clinical and healthcare data when used for the purposes envisaged in said article, that is, for judicial, epidemiological, public health, research or teaching purposes, except when the individual has given consent.

Similarly, the aforementioned provision appears in Decree 38/2012, of 13 March, on medical records and the rights and obligations of patients and healthcare professionals in relation to clinical documentation.

Article 16(2) of the decree stipulates:

> *"[….]*
>
> *2.– Access to medical records for the purposes specified in the previous section makes it necessary, in accordance with the provisions of Article 16(3) of Law 41/2002, of 14*

November, regulating patient autonomy and their rights and obligations in relation to clinical information and documentation, to store personal identifying data of patients separately from those of clinical or healthcare nature, such that as a general rule, anonymity continues to be safeguarded, except when patients themselves have consented to them not being separated."

[…]"

In line with the above, Osakidetza issued Instruction 1/2017 on the SYSTEM FOR PATIENT PERSONAL DATA PROTECTION FOR UNDERGRADUATE HEALTH SCIENCE STUDENTS ON TRAINING PLACEMENTS, HEALTH SCIENCE RESIDENTS AND RESEARCHERS in order to regulate the operating guidelines seeking to safeguard patients' right to privacy in the context of research.

Section 7.2 of the instruction stipulates the conditions for access to patient medical records in Osakidetza for epidemiological, public health, research or teaching purposes. Specifically, it states:

"The de-identification of data requires scientifically useful data (clinical and healthcare data, in our case) to be separated from those which make it possible to identify the person to whom they relate (medical record number, medical health card number, national identity number, etc.). Data must be de-identified by those who, being competent to do so, are subject to professional secrecy or another person with an equivalent duty of secrecy."

LAW ON BIOMEDICAL RESEARCH AND DATA PROTECTION AGENCY TENETS

Law 14/2007, of 3 July, on biomedical research is of interest as it includes definitions applicable to the subject analysed in this document.

Specifically, Article 3 of the law stipulates the following:

"Article 3. Definitions.

[…]

c) "Anonymization": the process by which it ceases to be possible by any reasonable means to draw a link between data and the person to whom they relate. This is also applicable to biological samples.

[…]

h) "Anonymous data": data recorded without a link to an identified or identifiable person

i) "Anonymized or irreversibly de-identified data": data that cannot be attributed to an identified or identifiable person due to destruction of the link with all information identifying the individual, or because such an attribution could only be obtained by unreasonable means, by which it is understood that it would require a disproportionately large amount of time, expense or effort."

This definition of anonymous or irreversibly de-identified data will be taken as a reference and applied in the current analysis in order to decide whether there is a link between data exchanged between the parties (as it has been destroyed or establishing such a link would require unreasonable means, understood as a disproportionately large amount of time, expense or effort) or not.

In line with the legislation presented, the tenets of Spanish Data Protection Agency indicate that the same criteria as those set out in the legislation of biomedical research should be applied to check whether an anonymization procedure has been carried out correctly.

A study on de-identification/anonymization of health-related data, published by the Agency's inspector general herself, Cristina Gómez Piqueras, indicates the criteria to be used to determine whether data has been properly de-identified:

"[…] Criteria for determining whether data have been de-identified can be extracted from the following conclusions: data and samples may be associated with personal data or may be anonymous from the outset; or alternatively may be associated with personal data and become anonymized, reversibly or irreversibly, through a de-identification process that destroys the link to the personal data.

Nevertheless, criteria that enable us to know whether we are working with personal or anonymous data can be specified.

The set of conditions outlined indicate the criteria that we should take into account to decide whether data or samples are de-identified, namely, that it would take:

- *Unreasonable means to identify a person,*

- *Disproportionate time*
- *Disproportionate expense*
- *Disproportionate effort*

[…]

LEGAL RELATIONSHIP BETWEEN THE ASSIGNOR AND ASSIGNEE

Unquestionably, the project is based on one of the crucial elements in matters of data protection, which needs particularly close attention and monitoring, namely, the assignment or transfer of data, a factor that makes it necessary to take considerable precautions throughout the lifetime of the project. In fact, Osakidetza hands over the data to BIOEF, and it can be stated from a legal perspective that the interaction framework is strong, with a formal structure that spans the full spectrum of the legislative tools, from the Law 14/2007, of 3 July, on biomedical research, that explicitly recognizes the existence of biobanks, legislators thereby covering a research need that was under-regulated, to Law 14/2011, of 1 June, on Science, Technology and Innovation, that responds to aspirations to consolidate and internationalize research in our setting, backing them with a legal framework. Furthermore, in the closest sphere, both geographically and organizationally speaking, the Additional Provision of Decree 135/2015, of 7 July, on the system for the authorization and operation of biobanks for biomedical research purposes in the Autonomous Region of the Basque Country, confirmed the steps for regulation, founding and management of such a resource previously followed in the case of the Basque Biobank, normalizing the activities carried out up to that point.

Narrowing the debate, and focusing on relationships in the public sector, in accordance with the Teckal criteria established by the Sentence of the Court of Justice of the European Community (now European Union), of 18 November 1999, Case C-107/98, it is assumed that there are bodies that provide services to public authorities that are not obliged to compete with private providers, as provided for both in the current Law 40/2015, of 1 October, on the legal framework for the public sector, and the new Law 9/2017, of 8 November, on public sector contracts, by which the Directives 2014/23/EU and 2014/24/EU, of 26 February 2014 of the European Parliament and Council are transposed into Spanish law. The relationship between Osakidetza and BIOEF as well as the transfer of de-identified data are underpinned by the COLLABORATION AGREEMENT BETWEEN OSAKIDETZA AND THE BASQUE FOUNDATION FOR HEALTH INNOVATION AND RESEARCH FOR THE MANAGEMENT OF THE BASQUE BIOBANK FOR RESEARCH, of 3 April 2009, and the COLLABORATION AGREEMENT BETWEEN THE PUBLIC BODY OSAKIDETZA/BASQUE HEALTH SERVICE AND THE BASQUE FOUNDATION FOR HEALTH INNOVATION AND RESEARCH ON THE MANAGEMENT OF FUNDS FOR SUPPORTING RESEARCH ACTIVITIES, of 16 October 2006. Both of these agreements cover the handling of anonymized data exchanged between the cited parties.

Prior identification of risks

In line with the aforementioned, it has been decided which items should be controlled in accordance with the circumstances.

The objective of the current analysis is to determine whether the anonymization procedure has been carried out properly and whether it is possible to identify individuals based on the information sent by Osakidetza to BIOEF.

The variables for identifying risks to be used to detect situations of vulnerability, and hence, that might potentially lead to the identification of individuals directly or indirectly based on the information processed by BIOEF, will be those set out in the following table abiding by the tenets of the Spanish Data Protection Agency:

IDENTIFICATION VARIABLES		
TYPE OF DATA	**DETAIL**	**EXAMPLE**
MICRODATA	Any types of characteristics that in themselves make it possible to identify a given individual	Names, surnames, national identity numbers, photographs, other codes
INDIRECTLY IDENTIFYING DATA	Cross-referenced data from different sources that may make it possible to trace the identity of individuals	The combination of sex, age, place of birth and diagnosis with a particular health condition may enable the indirect identification of a given individual
SENSITIVE DATA	Health-related data	Diagnosis, medications prescribed, tests, etc.
NON-IDENTIFYING DATA	Data containing no personal information, with which it is not possible to identify individuals	Countries, drugs, etc.
OTHER CONFIDENTIAL DATA	Any other type of data not covered by the other categories	

In this way, all the categories of data or specific data to be processed by BIOEF will be assessed and assigned to a category, indicating whether they are microdata or might allow indirect identification, or otherwise should be considered sensitive or some other type of confidential data not covered by the other categories.

Subsequently, said information will be subject to a risk analysis following the method indicated in Section 3.2 of this document.

The criteria that determine the likelihood of being able to identify an individual are those indicated in the tenets, that is, the combination of reasonable means required, and whether it would involve disproportionate time invested, expenses incurred and effort made.

4.2. RISK ANALYSIS

The data subject to analysis in the following tables have been extracted from the documents submitted by BIOEF. In this case, each type of data in its own right has been analysed in detail; there are relatively few and all are well-defined and identified.

Table of risk analysis

HUMAN METADATA (videos) / **METADATA associated with videos of colonoscopies in HUMANS**		**Identifying data**	**Likelihood**	**Severity (Impact)**	**Risk score**	**Level of risk**	**Corrective measures**
CODE	Numerical code linking the video/lesion with associated data. This code never makes reference to the patient.	Non-identifying data	1	1	1	Marginal	
NUMBER OF POLYPS OF INTEREST (N)	Number of polyps of interest found in a given patient. (Example: 3)	Non-identifying data	1	1	1	Marginal	
CURRENT POLYP ID (X/N)	Number assigned to the polyp of interest (e.g., if a patient has 3 polyps, polyp 1 of 3 (1/3), 2 of 3 (2/3), and 3 of 3 (3/3))	Non-identifying data	1	1	1	Marginal	
POLYP SIZE (mm)	Diameter of polyp of interest in mm	Non-identifying data	1	1	1	Marginal	
PARIS CLASSIFICATION	A system for classifying polyps according to their morphology: elevated lesions (polypoid)-	Non-identifying data	1	1	1	Marginal	

	pedunculated or sessile; flat elevated lesions; flat lesions.						
NICE CLASSIFICATION (NBI Vascular pattern)	A system for classifying polyps according to their vascular pattern: type 1 (hyperplastic polyp); type 2 (adenoma); or type 3 (deep submucosal invasion or cancer).	Non-identifying data	1	1	1	Marginal	
PRELIMINARY DIAGNOSIS (Gastroenterologist)	Macroscopic diagnosis by gastroenterologist at the time of the endoscopy: hyperplasia, adenoma, or adenocarcinoma.	Indirectly identifying data	1	1	1	Marginal	
LITERAL DIAGNOSIS (Pathologist)	Diagnosis of the pathologist after histological analysis of the lesion: hyperplasia, adenoma, or adenocarcinoma.	Indirectly identifying data	1	1	1	Marginal	
HISTOLOGICAL STRATIFICATION	Indication of lesion characteristics at the histological level: no dysplasia, low grade dysplasia, high grade dysplasia, invasive adenocarcinoma, hyperplasia, or serrated morphology.	Indirectly identifying data	1	1	1	Marginal	
ADDITIONAL FINDINGS	Notes of interest concerning the lesion that may be added by the gastroenterologist or the pathologist.	Indirectly identifying data	1	1	1	Marginal	

HUMAN METADATA (images) / METADATA associated with the optical coherence or multi-photon tomography images taken in HUMAN tissue Data analysed		Identifying data	Likelihood	Severity (Impact)	Risk score	Level of risk	Corrective measures
CODE	Numerical code linking the video/lesion with associated data. This code never makes reference to the patient.	Non-identifying data	1	1	1	Marginal	
AGE	Age	Non-identifying data	1	1	1	Marginal	
SEX	Man, woman.	Non-identifying data	1	1	1	Marginal	
REASON FOR COLONOSCOPY	Screening colonoscopy; urgent colonoscopy for altered bowel habit, surveillance; therapy.	Non-identifying data	1	1	1	Marginal	
COLONOSCOPY DATE_TIME	Date and time of the colonoscopy	Non-identifying data	1	1	1	Marginal	
NUMBER OF POLYPS FOUND (N)	Number of polyps of interest found in a given patient. (Example: 3)	Non-identifying data	1	1	1	Marginal	
CURRENT POLYP ID (X/N)	Number assigned to the polyp of interest (e.g., if a patient has 3 polyps, polyp 1 of 3 (1/3), 2 of 3 (2/3), and 3 of 3 (3/3))	Non-identifying data	1	1	1	Marginal	
POLYP SIZE (mm)	Diameter of polyp of interest in mm	Non-identifying data	1	1	1	Marginal	
POLYP LOCALIZATION	Ascending colon; transverse colon; descending colon; sigmoid colon; rectum	Sensitive data	1	1	1	Marginal	

KUDO´S PIT PATTERN	A classification system based on the appearance of the colon mucosa, it classifies polys, differentiating them into neoplastic or non-neoplastic, according to crypt morphology and pit size.	Sensitive data	1	1	1	Marginal	
PARIS CLASSIFICATION	A system for classifying polyps according to their morphology: elevated lesions (polypoid)-pedunculated or sessile; flat elevated lesions; or flat lesions.	Non-identifying data	1	1	1	Marginal	
NICE CLASSIFICATION (NBI Vascular pattern)	A system for classifying polyps according to their vascular pattern: type 1 (hyperplastic polyp); type 2 (adenoma); or type 3 (deep submucosal invasion or cancer).	Non-identifying data	1	1	1	Marginal	
BOSTON BOWEL PREPARATION SCALE	A numerical scale used to assess the adequacy of bowel cleansing, where 0 indicates inadequate; 1, poor; 2, good and 3, excellent.	Sensitive data	1	1	1	Marginal	
MORPHOLOGIC DIAGNOSIS (SNOMED Code)	Diagnostic codes based on the morphology of the lesion using the Systematized Nomenclature of Human Medicine (SNOMED) codes. (e.g., M-81443: Low grade adenocarcinoma)	Sensitive data	1	1	1	Marginal	

TOPOGRAPHIC DIAGNOSIS (SNOMED Code)	Diagnostic codes based on the localisation of the lesion using the Systematized Nomenclature of Human Medicine (SNOMED) codes (e.g., T67010- Colon, splenic flexure)	Non-identifying data	1	1	1	Marginal	
PRELIMINARY DIAGNOSIS (Gastroenterologist)	Macroscopic diagnosis by gastroenterologist at the time of the endoscopy: hyperplasia, adenoma, or adenocarcinoma.	Indirectly identifying data	1	1	1	Marginal	
LITERAL DIAGNOSIS (Pathologist)	Diagnosis of the pathologist after histological analysis of the lesion: hyperplasia, adenoma, or adenocarcinoma.	Indirectly identifying data	1	1	1	Marginal	
HISTOLOGICAL STRATIFICATION	Indication of lesion characteristics at the histological level: no dysplasia, low grade dysplasia, high grade dysplasia, invasive adenocarcinoma, hyperplasia, or serrated morphology.	Indirectly identifying data	1	1	1	Marginal	
PREVIOUS TREATMENT	Yes; No.	Non-identifying data	1	1	1	Marginal	
RECURRENCE	Yes; No.	Sensitive data	1	1	1	Marginal	
ADDITIONAL FINDINGS	Notes of interest concerning the lesion that may be added by the gastroenterologist or the pathologist.	Indirectly identifying data	1	1	1	Marginal	

4.3. Personal data processing operations

Having completed the risk analysis, the following table sets out whether the principles, safeguards and technical or organizational measures included in current data protection legislation are applicable to the data processing operations undertaken by BIOEF using the data received from Osakidetza.

AREA SUBJECT TO CONTROL	DETAIL	EVALUABLE / RATIONALE
Principles and safeguards	– Legality, loyalty and transparency – Legality of the processing	Not evaluable; no processing of personal data has been detected
Consent	– Consent – Consent for minors	Not evaluable; no processing of personal data has been detected
Purpose of the processing		Not evaluable; no processing of personal data has been detected
Duty of disclosure and exercise of rights	– Duty of information – Obligation to pay fees – Attention to rights – Blocking of data	Not evaluable; no processing of personal data has been detected
Duty of confidentiality		Not evaluable; no processing of personal data has been detected
Special categories of data		Not evaluable; no processing of personal data has been detected
Processing of data concerning criminal or administrative offences	– Criminal offences and sentences – Administrative offences and sanctions	Not evaluable; no processing of personal data has been detected
Controller of the processing	– Organizational security measures – Processing operations	Not evaluable; no processing of personal data has been detected

	– Security violations	
Security measures	– Technical security measures – Representative of the entity from outside the European Union	Not evaluable; no processing of personal data has been detected
Data processor	–	Not evaluable; no processing of personal data has been detected
Data protection officer	–	Not evaluable; no processing of personal data has been detected
Certifications and monitoring bodies	– Use of seals and certificates – Certification providers and supervisory bodies	Not evaluable; no processing of personal data has been detected
International data transfer	–	Not evaluable; no processing of personal data has been detected
Regulatory authorities	– Failure to comply with decisions of regulatory authorities – Inspection by regulatory authorities – Notification of security violations – Prior consultation	Not evaluable; no processing of personal data has been detected
Right to privacy and secrecy of communications	– Performance monitoring – Surveillance for security purposes	Not evaluable; no processing of personal data has been detected

5. CONCLUSIONS

The ARTICLE 29 WORKING PARTY OPINION 05/2014 on anonymization techniques, adopted on 10 April 2014 states,

> *"On many occasions, a set of anonymized data may pose residual risks for the interested parties. That is, even when it is not possible to recover the specific record for an individual, it may be possible find out information about him or her with the help of other available sources of information (public domain or not). It should be underlined that, beyond the direct effects that an inadequate anonymization procedure may have on the individuals involved (hassle, loss of time, feeling of loss of control on being included in a group without their knowledge or having given prior consent), it is also possible that there will be secondary indirect effects due to inadequate anonymization if a hacker, given that they are anonymized data, erroneously targets a given individual. Such secondary effects would emerge if the intentions of the hacker were to be malicious. Given all this, the Working Party would like to underline that anonymization techniques can safeguard privacy but only if they their application is correctly designed, meaning that there is a need to clearly define prerequisites (the context) and the goals of the process to obtain the desired level of anonymization. […]"*

The Article 29 working party, in their Opinion 05/2014 on anonymization techniques, states that there is always a residual risk of the identification of an individual even after the application of various anonymization techniques.

Osakidetza has carried out a first layer of anonymization of the data to be processed for the purposes of sending them to BIOEF under the framework of the PICCOLO project.

In this report, a risk analysis of the data sent to BIOEF has been presented seeking to check whether it is necessary to add a second layer of anonymization to provide stronger guarantees of confidentiality and safeguarding of the privacy of individuals from whom the original data are gathered.

In relation to this, the following conclusions can be drawn based on the risk analysis presented in Section 4 of the report:

First. Having completed the risk analysis, no situations for which it would be necessary to perform a second layer of anonymization have been detected, even though it would always be mandatory to maintain close monitoring and a high level of awareness to ensure identification of any risk that may arise.

Second. Similarly, data protection would not generally apply to the information resulting from the application of a layer of anonymization, and hence, as indicated in Section 4.4, it is not possible to detect risks in relation to compliance with the principles, safeguards and safety measures included in current data protection legislation, in particular, in European Data Protection Regulation.

Annex 6

Amendment Ethical Approval (BIOEF), June 2018

Issued by: Euskadi Clinical Research Ethics Committee

CEIm
Euskadiko Medikamentuen gaineko Ikerkuntza Batzorde Etikoa
Comité de Ética de la Investigación con medicamentos de Euskadi

EUSKO JAURLARITZA
GOBIERNO VASCO
OSASUN SAILA
DEPARTAMENTO DE SALUD

INFORME DEL COMITE DE ETICA DE LA INVESTIGACION CON MEDICAMENTOS DE EUSKADI (CEIm-E)

Arantza Hernández Gil
Secretaria del CEIm de Euskadi (CEIm-E)

CERTIFICA

Que este Comité de acuerdo a la ley 14/2007 de Investigación Biomédica, principios éticos de la declaración de Helsinki, el Real Decreto 1716/2011, de 18 de noviembre, por el que se establecen los requisitos básicos de autorización y funcionamiento de los biobancos con fines de investigación biomédica y del tratamiento de las muestras biológicas de origen humano, y se regula el funcionamiento y organización del Registro Nacional de Biobancos para investigación biomédica y resto de principios éticos aplicables, en su reunión del día 21/03/2018, acta Acta 03/2018, ha evaluado la propuesta del promotor para que se realice la modificación "recogida de vídeos de pacientes que no participen en el Cribado de Cáncer de colon" en el estudio:

Título: Multimodal highly-sensitive photonics endoscope for improved in-vivo colon cáncer diagnosis and clinical decision support - PICCOLO

Código Promotor: 17-14 Código Interno: PI+CES BIOEF 2017-03

Versión Hoja Información al Paciente evaluada: GENERAL / V3, 30/08/17
VIDEO / V3 19 de Marzo 2018

Y que este Comité ha decidido emitir **INFORME FAVORABLE** A LA REALIZACIÓN DE DICHA ENMIENDA

Lo que firmo en Vitoria, a 13 de abril de 2018

ARANTZAZU HERNANDEZ GIL

Firmado digitalmente por ARANTZAZU HERNANDEZ GIL
Nombre de reconocimiento (DN): c=ES, o=Eusko Jaurlaritza, ou=SALUD, ou=Ziurtagiri onartua - Certificado reconocido, ou=Entitate publikoen ziurtagiri - Certificado de entidad publica, ou=Condiciones de uso en www.izenpe.com nola erabili jakiteko, dnQualifier=-dni 44678219Y -cif S4833001C, cn=ARANTZAZU HERNANDEZ GIL, givenName=ARANTZAZU, sn=HERNANDEZ, serialNumber=44678219Y
Fecha: 2018.04.13 09:50:22 +02'00'

Arantza Hernández Gil
Secretaria del CEIm de Euskadi (CEIm-E)

Nota: Una vez comenzado el estudio, se recuerda la obligación de enviar un **informe de seguimiento anual** e **informe final** que incluya los resultados del estudio (si el estudio dura menos de un año, con el informe final será suficiente). Más información en la página web del CEIm-E:
http://www.osakidetza.euskadi.eus/informacion/proyectos-de-investigacion/r85-pkfarm03/es/