

UPSIDE

Deliverable D7.4

Grant Agreement No.	101070931
Start date of Project	1 September 2022
Duration of the Project	48 months
Deliverable name	D7.4 Data Management Plan – V2
Partner Leader	TUD
Dissemination Level	PU

<i>Status</i>	Intermediate
<i>Version</i>	V2.0
<i>Submission Date</i>	28-02-2025





<i>Author(s)</i>	Tiago Costa (TUD) Eva Kassotaki (TUD)
<i>Co-author(s) and Contributors</i>	Thomas Andrae (FUSF) Dante Muratore (TUD) Wouter Serdijn (TUD) Georgios Spyropoulos (UG) Máté Döbrössy (UF) Marcelino Santos (SG) Manuel Martina (MST) Mattia Arlotti (NWK)

European
Innovation
Council



Funded by the European Union. Views and opinions expressed are however those of the author(s) only and do not necessarily reflect those of the European Union or the granting authority. Neither the European Union nor the granting authority can be held responsible for them.

House Style

	Red RGB	Green RGB	Blue RGB	HEX
				
Pink	247	181	192	#F7B5C0
Grey	161	161	161	#A1A1A1
Blue	41	171	226	#29ABE2
 <p>THE USE OF THE EU EMBLEM IN THE CONTEXT OF EU PROGRAMMES 2021-2027 LINK</p> <p>In addition to the obligations set out in Article 17, communication and dissemination activities as well as infrastructure, equipment or major results funded under EIC actions must also display the following special logo:</p> <p>   </p>				
EU corporate blue	0	51	153	#003399
Yellow	255	204	0	#FFCC00

Quality Control

Author	Name	Date
WP leader	Thomas Andreae	19-02-2023
Internal reviewer	Wouter Serdijn	19-02-2023
Coordinator	Tiago Costa, Eva Kassotaki	28-02-2025

History of Changes

Version	Change made	Date
V1.0	Submitted Version M6	28-02-2023
V2.0	Final updated version for V2.0	28-02-2025

Table of Contents

Executive Summary.....	4
Summary of the updates in this version (M30)	4
1. Overview of the Project	5
1.1 Project abstract	5
2. Data summary.....	6
2.1. Provide a summary of the data addressing the following issues:	6
2.1.1. State the purpose of the data collection/generation	6
2.1.2. Explain the relation to the objectives of the project	6
2.1.3. Specify the types and formats of data generated/collected & the origin of the data	6
2.1.4. Specify if existing data is being re-used (if any)	8
2.1.5. State the expected size of the data (if known).....	8
2.1.6. Outline the data utility: to whom will it be useful.....	8
3. Making data findable, including provisions for metadata [FAIR data]	12
3.1 Making data findable, including provisions for metadata	12
3.2. Making data openly accessible	13
3.3. Making data interoperable	13
3.4. Increase data re-use (through clarifying licenses)	13
4. Allocation of resources	14
5. Data Security.....	15
6. Ethical aspects.....	15
6.1. Animals	16
6.1.1. The rationale for using animals - Status update from UGhent and UF.....	16
6.1.2. Planned experiments and animal numbers.....	16
6.1.3. The 3Rs: Reduction, Replacement, Refinement.....	17
6.2. Humans.....	17
6.3. Human cells/tissues.....	18
6.4. Non-EU countries.....	18
7. Other	18

List of Tables:

Table 1: Upside data and its purpose of collection.....	6
Table 2: Upside relation of data collection to objectives	6
Table 3 Types, formats, purpose and access details of data collected and processed within UPSIDE.....	8
Table 4: Scale of the magnitude of collected/generated data within UPSIDE	8
Table 5: How data will be shared between UPSIDE partners	9
Table 6: How data will be shared with UPSIDE stakeholders (target groups 2,3 and 4)	11
Table 7: In place policies for data management from partners	18

Abbreviations

WP : Work Package

DMP: Data Management Plan

CMOS: Complementary Metal-Oxide-Semiconductor

GA: Grant Agreement

CA: Consortium Agreement

DoA: Description of Action

MDD: Major Depressive Disorder

EIC: European Innovation Council

CMOS: Complementary metal oxide semiconductor

EEG: Electroencephalogram

FAIR: Findability, Accessibility, Interoperability, and Reusability

SME: Small Medium Enterprise

C&D: Communication and Dissemination

EC: European Commission

TRD: Treatment-Resistant Depression

ECT: Electroconvulsive therapy

tRMS: repetitive Transcranial Magnetic Stimulation

VNS: Vagus nerve stimulation

DBS: deep brain stimulation

tFUS: transcranial focused ultrasound

NT: Neuromodulation-based Therapy

eFUS: epidural focused ultrasound

EBI: epidural brain interface

Executive Summary

UPSIDE Data Management Plan (DMP) outlines how research data will be collected, processed, stored, and shared throughout this research project.

The purpose of this DMP is to ensure that the research data is managed in a way that is consistent with good practice and at the same time complies with ethical and legal requirements. Therefore, this DMP is an important tool for UPSIDE researchers, as it helps to clarify the data management process of the project, and it provides a framework for ensuring that data is properly preserved and accessible for future use. This DMP–V2 is the second release (M30) for UPSIDE, which builds on its original release on M6.

Further elaborated and final version will be submitted at the end of the project in M48, while updates on the status of its implementation will be briefed in the project’s EC Periodic Reports. This document is developed based on standardized reporting documentation within TU Delft.

Summary of the updates in DMP M30 Version

The key updates included in this version cover:

- Additional descriptions, particularly for the WP5 data but also for other WPs, in Chapter 2 (2.1.3, 2.1.5);
- Additional descriptions to more clearly explain what data generated in the project will be openly shared with the research community and how this will be done as requested by the evaluators in the Periodic Report 1, in Chapter 2 (2.1.6) and particularly Table 6;
- Updates on implementation in compliance with permits and procedures in place for the animal experiments and the conduction of the focus groups, in Chapter 6;
- Textual improvements and alignment updates in the document for consistency purposes throughout the different chapters.

1. Overview of the Project

Title: UPSIDE

Start date: 01-09-2022

End date: 31-08-2026

Grant number / URL: <https://cordis.europa.eu/project/id/101070931>

1.1 Project abstract

Major depressive disorder (MDD) is the leading cause of disability worldwide, affecting 300 million people with a lifetime prevalence of 15%. Approximately one third of all MDD patients fail to respond to currently established treatments based on medication and psychotherapy, thus falling into the category of Treatment-Resistant Depression (TRD) patients. Electroconvulsive therapy (ECT), repetitive Transcranial Magnetic Stimulation (rTMS), Vagus nerve stimulation, deep brain stimulation (DBS) and transcranial focused ultrasound (tFUS) are not practical for repetitive treatments (tFUS), still show poor spatial resolution (ECT, rTMS) or low network coverage (VNS, DBS), with average remission rates in clinical trials still lower than 30 %. Apart from the existing stimulation hurdles, reliable biomarkers for depression are needed as a diagnostic tool, and, in the case of Neuromodulation-based Therapy (NT), to determine the stimulation efficacy and allow for personalized treatment. The UPSIDE project proposes a minimally-invasive, high spatial resolution and multi-brain region stimulation and recording system to largely exceed the capabilities of existing NT for depression. Our objective is to research and validate in vivo a hybrid neurotechnology consisting of an epidural focused ultrasound (eFUS) stimulator employing three-dimensional beamforming, and a high-density epidural EEG recording system. Epidural deployment of these devices will be enabled by novel methods for massive integration and miniaturization of high performing piezoelectric ultrasound materials and high-fidelity organic bioelectronic materials with high energy-efficient complementary metal-oxide semiconductor (CMOS) technology in a biocompatible manner. The UPSIDE project will result in a demonstrator which will allow, for the first time, network stimulation and simultaneous biomarker readout in behavioural experiments with animal models featuring depression-like symptoms. This technological breakthrough will pave the way towards a personalized treatment for TRD.

2. Data summary

2.1. Provide a summary of the data addressing the following issues:

2.1.1. State the purpose of the data collection/generation

The table below explains the purpose of data collection and generation per relevant WP:

WP	Purpose
WP1	Laboratory data for the development of the CMOS technology components of the UPSIDE system
WP2	Laboratory data related to the organic bioelectronics components of the UPSIDE solution
WP3	Data is generated by laboratory measurements to validate the UPSIDE system-level integration
WP4	Data is generated by laboratory measurements for pre-clinical validation of the UPSIDE system
WP5	Laboratory data for biomarker signal detection for depression
WP6	Administrative data collected for management purposes where privacy is covered by the Consortium Agreement

Table 1: Upside data and its purpose of collection

2.1.2. Explain the relation to the objectives of the project

The objectives of UPSIDE are explained below in relation to each WP, towards a full proof-of-concept EBI:

WP	Relation to objectives
WP1	Design & process data and measurements related to energy-efficient CMOS circuits for interfacing with 2D arrays of ultrasound transducers and organic neural recording arrays
WP2	Design & process data related to: 1 The development of conformable polymer-based passive MEAs with ultra-low impedance; 2. The Development of IGT-arrays for on spot amplification of neurophysiological signals.
WP3	Design and testing data related to integrated ultrasound transducers and organic neural recording arrays with the CMOS interfaces in a biocompatible and flexible epidural system, to achieve a full EBI
WP4	Laboratory data related to the assessment of the safety and efficacy of the EBI in addressing depression-like symptoms in vivo, in behavioural rat models of depression
WP5	Modelling and testing data related to neural signal decoding tools to identify depression biomarkers to enable personalized therapy for depression

Table 2: Upside relation of data collection to objectives

The UPSIDE consortium needs to establish a Data Management Plan (DMP) that supports the project partners in adopting the right policy concerning the collection, generation and sharing of the data. Furthermore, this DMP outlines the framework under which the developed project tools, methods and resources will be made openly available as much as possible, yet as close as necessary in line with the project's GA, CA and commercially sensitive-related limitations.

2.1.3. Specify the types and formats of data generated/collected & the origin of the data

The table below illustrates the types, formats, purpose and access details of data collected and processed within UPSIDE per WP:

WP	Type of data	File formats	Origin of data	Purpose of processing	Storage location	Who will have access to the data
WP1	Device data	.csv .pdf	collected during testing of CMOS	Simulation results of device	TU Delft UPSIDE project server	TU Delft UPSIDE research team
WP1, WP3	Application data	.pcbdoc .gds	collected during design of CMOS or system level	Accurate outline of device or system	TU Delft UPSIDE project server & SURFDrive when validated as necessary	TU Delft UPSIDE research team & Project partners upon request
WP1, WP3	simulation and testing data	.csv .pdf	collected during release of CMOS device or integrate system validation	Performance of device or system	TU Delft UPSIDE project server & SURFDrive when validated as necessary	TU Delft UPSIDE research team & Project partners upon request
WP2	Device data, schematics, electrophysiology data	.txt, .doc, .ppt, .jpeg, .eps, .png, .mat, .csv data, .dat, .gds, .brd, .sch	collected during design and testing of neural interfaces and electrophysiology	Accurate outline of device or system	UGENT UPSIDE project server, OneDrive and Google Drive	UGENT UPSIDE research team and UF
WP4	images	.jpeg .pdf	collected during the histological analysis	characterization of FUS device performance	UF UPSIDE project server; transfer to SURFDrive on request	UF UPSIDE research team, and Project partners upon request
WP4	electrophysiology / Fibre Photometry	.mat	collected during biological validation of the device	characterization of the biological impact of FUS device	UF UPSIDE project server; transfer to SURFDrive on request	UF UPSIDE research team, and Project partners upon request
WP4	behavioural	.xls, .mp4 .jnb, .pzf	collected during behavioural analysis	characterization of behavioural impact of FUS device	UF UPSIDE project server; transfer to SURFDrive on request	UF UPSIDE research team and NWK, and Project partners upon request
WP5	Laboratory data	.m, .mat, .py, .json	Collected during the analysis of electrophysiological signals for	Extraction of significant data features	NWK UPSIDE project servers and	NWK UPSIDE research team, and Project partners

			biomarker extraction. Collected during analysis for biomarker signals	related to depression condition. Detection of depression.	SharePoint; transfer to SURFDrive on request	
WP1, WP2, WP3, WP4, WP5, WP6, WP7, WP8	project deliverables & public reports	.doc .pdf .png .jpeg	deliverable reports generated as project results	achieving project results	Partners' servers & OneDrive, TEAMS UPSIDE group, UPSIDE website, CORDIS	general audience

Table 3 Types, formats, purpose and access details of data collected and processed within UPSIDE

2.1.4. Specify if existing data is being re-used (if any)

There is a possibility that pre-existing data to validate the accuracy of the UPSIDE devices or results will also be used as a reference point for comparison and validation of the accuracy of their performance. The equivalent project teams have already access to such data and provisions for access as this comes from in-house previous research results.

2.1.5. State the expected size of the data (if known)

The table below lists the type of software used and the approximate size per relevant WP, along with a remark for any file size-related concerns. The size estimations are rough.

WP	Software or device/tool	Total Size	file size concern when applicable
WP1	Cadence Virtuoso	50 GB	
WP3	Altium Designer	10 GB	
WP2	Keysight, oscilloscope, openephys system, palmsens, Matlab, adobe illustrator, MS excel, MS word	100GB	.dat files can be very big (15Ks/s > 60' 10GB)
WP4	MATLAB, Adobe PhotoShop, Image J, Biobserve, Microsoft Office, Statistica, GraphPad	100GB	Microscopic pictures can be very large, ePhys data
WP5	Matlab, Git, Pycharm	100GB	Each dataset is around 5 GB

Table 4: Scale of the magnitude of collected/generated data within UPSIDE

For data transferring between the UPSIDE partners during the project duration, SURFdrive will be employed when necessary which has a capacity of up to 500GB. However, primary raw data generated from partners will be stored in the local institutional servers of each partner and only data related to the needed interactions and integrations required for achieving the UPSIDE solution will be uploaded in SURFdrive upon request.

For providing public access, Zenodo, 4TU.ResearchData and GitHub will be utilized. Additionally, data will be shared through publications and conferences, featuring drawings and schematics.

2.1.6. Outline the data utility: to whom will it be useful

The below-targeted stakeholders are the ones to whom potential UPSIDE data can also be useful in line with the project's Communication and Dissemination strategy:

1. The UPSIDE partners as co-workers towards achieving UPSIDE's solution for securing system-level integration:

How data is shared	When data is shared	Who will be able to use	Restrictions in place	Facilitation of re-use
SURFDrive, OneDrive, SharePoint, emails, GitHub	as soon as considered accurate upon request	UPSIDE partners	Metadata in place will describe any required software	Metadata in place will provide a description of required information for potential utilization and use

Table 5: How data will be shared between UPSIDE partners

2. The scientific community working in the field of Biomedical CMOS circuits and systems, organic bioelectronics, brain-computer interfaces and neurobiology.

3. Commercial stakeholders in the field of circuit design, implantable devices, brain-machine interfaces, microsystem integration, focused ultrasound neuromodulation, ultrasound technology, semiconductors and neural interfaces.

4. The medical community in the fields of neurology, neurosurgery and psychiatry.

How data is shared	When data is shared	What is the main data useful to the community?	Who will be able to use	Restrictions in place	What can be shared	Facilitation of re-use
<p>Zenodo, GitHub, 4TU.ResearchData, publications, conferences, project website, social media, newsletters.</p>	<p>As soon as final, in accordance with the publishing journal's data sharing policy, embargo and patent filing application restrictions, or at the end of the project.</p>	<p>WP1 Schematics, Layout in Cadence files</p> <p>WP2 Schematics, electrophysiology data</p> <p>WP3 Relay station schematics/layout</p> <p>WP4 Codes for data processing</p> <p>WP5 Code Libraries</p>	<p>Group 2,3 and 4 when interested</p>	<p>WP1: Cadence files and measurements results are protected by NDA,, therefore can be shared only with the people under this NDA (TUD), Patent application KER1, Confidential deliverables</p> <p>WP2: Patent application KER3, Confidential deliverables</p> <p>WP3 Patent application KER3, KER4, Confidential deliverables</p> <p>WP4 Files and image sizes</p> <p>WP5 Patent application KER5, Confidential deliverables & IP</p>	<p>WP1: Drawings of schematic, some PCB design files</p> <p>WP2: Schematics, Designs, Graphs, Electrophysiology data, Protocols, matlab codes</p> <p>WP3 Some PCB schematics and layouts</p> <p>WP4: Implantation protocol, 3D print data headpiece etc., vocalisation data, ePhys data, fiber photometry data</p> <p>WP5 Open source or restricted access API libraries and source code, physiological related foreground knowledge. Zenodo as an open source database is accessible trough API,</p>	<p>Metadata in place will describe required information for potential re-use</p>

					Matlab and Python functions will be shared through GitHub. API on GitHub, both for processing and recalling data	
--	--	--	--	--	--	--

Table 6: How data will be shared with UPSIDE stakeholders (target groups 2,3 and 4)

3. Making data findable, including provisions for metadata [FAIR data]

3.1 Making data findable, including provisions for metadata

- *Outline the discoverability of data (metadata provision)*
- *Outline the identifiability of data and refer to standard identification mechanism. Do you make use of persistent and unique identifiers such as Digital Object Identifiers?*
- *Outline naming conventions used*
- *Outline the approach towards search keyword*
- *Outline the approach for clear versioning*
- *Specify standards for metadata creation (if any). If there are no standards in your discipline describe what metadata will be created and how*

Data/code that can be publicly released will be published in Zenodo, 4TU.ResearchData or GitHub. Both Zenodo and 4TU.ResearchData are trusted data archives which ensure the published datasets will be findable and accessible in the long term (>10 years from the publication date). These archives assign a persistent identifier (Digital Object Identifier DOI), which makes the datasets citable and persistently available. The 4TU.ResearchData archive in particular also uses OPeNDAP for NetCDF data which facilitates the findability and inspection of NetCDF records. Although GitHub does not provide a DOI directly, a DOI to the GitHub repository can be assigned through Zenodo.

Data/code that will not be publicly released will be stored within the respective owner's institutional archive, and accessible to the employees of the respective institution.

Data files are advised to be named using the following elements in the file name:

- Date: YYYYMMDD
- V0.1=draft version, v1.0=final version, V1.1=draft updated version, V2.0=updated final version
- Descriptive file name
- Initials of the person who last modified the file (for internal use)

UPSIDE uses different naming conventions for all research data,

where: x = WP number, y = Deliverable number and finally a version number

Example: 20230306_UPSIDE-WPx_Dy.y_Title_v0.1

In addition to filling in these fields and to salient keywords for searchability and DOI for publications, metadata will also include the following information:

- the name of the action, acronym and grant number (EIC-PATHFINDER, UPSIDE, 101070931)

- the publication date, and length of the embargo period if applicable
- a "keyword" category will be systematically included in the metadata file. Relevant keywords following the Library of Congress subject Headings (LCSH) will be added when relevant in the citation metadata.

3.2. Making data openly accessible

- *Specify which data will be made openly available? If some data is kept closed provide rationale for doing so*
- *Specify how the data will be made available*
- *Specify what methods or software tools are needed to access the data? Is documentation about the software needed to access the data included? Is it possible to include the relevant software (e.g. in open source code)?*
- *Specify where the data and associated metadata, documentation and code are deposited*
- *Specify how access will be provided in case there are any restrictions*

Not all data will be made publicly available. Data/code that will remain close is the commercially sensitive data. Thus, such data will be shared among relevant collaborators for the purposes of this project only and in accordance with the project's DoA and CA.

As far as is necessary to ensure the reproducibility of public results, data created in this project as parts of public deliverables will be made openly available via Zenodo, 4TU.ResearchData and GitHub. All datasets will be accompanied by README files providing all necessary information about the access to the software needed to access the data. Proprietary software itself cannot be publicly shared. However, the version used will be indicated in the metadata.

3.3. Making data interoperable

- *Assess the interoperability of your data. Specify what data and metadata vocabularies, standards or methodologies you will follow to facilitate interoperability.*
- *Specify whether you will be using standard vocabulary for all data types present in your data set, to allow inter-disciplinary interoperability? If not, will you provide mapping to more commonly used ontologies?*

In order to facilitate data interoperability to the highest possible extent, we will furthermore:

- Clearly define all terms in each report and publication produced.
- All documentation included in the datasets is provided as a README file in plain text format (.txt).

3.4. Increase data re-use (through clarifying licenses)

- *Specify how the data will be licenced to permit the widest reuse possible*
- *Specify when the data will be made available for re-use. If applicable, specify why and for what period a data embargo is needed*

- *Specify whether the data produced and/or used in the project is useable by third parties, in particular after the end of the project? If the re-use of some data is restricted, explain why*
- *Describe data quality assurance processes*
- *Specify the length of time for which the data will remain re-usable*

All datasets that are not commercially sensitive will be licensed under a CC-BY license, requiring attribution/credit for the original creation while ensuring the broadest possible re-use. Related datasets will be made publicly available upon the publication of the corresponding research papers resulting from this study, in accordance with the journal's data-sharing policy. However, data related to IP applications resulting from the UPSIDE project will be under embargo during the IP application process until the application is granted. During the embargo period, access to the datasets will be restricted. Additionally, data related to layouts in Cadence files from WP1 are restricted to access and use only by the TUD team members under an NDA. Therefore, this data cannot be shared.

4TU.Center for Research Data ensures data quality and curation (manual curation at the time of deposition, and automated curation and checks for data integrity after the deposit). Research data will be available for at least 15 years from the time of data deposition.

The following checklist will be used as a reference for data quality:

- Datasets should be deposited in a proper archive if published, or in a secure institutional storage if not published.
- Datasets should follow the naming convention of paragraph 3.1 above.
Also suggested basic rules are encouraged:
 - do not use only numbers to name files;
 - avoid the use of white spaces in file/directory names;
 - separate data files from code files (e.g. in different sub-directories);
 - distinguish datasets per processing level (raw data, processed data, visualizations, finalized data).
- Datasets must have at least a README file.

4. Allocation of resources

Explain the allocation of resources, addressing the following issues:

- *Estimate the costs for making your data FAIR. Describe how you intend to cover these costs*
- *Clearly identify responsibilities for data management in your project*
- *Describe costs and potential value of long term preservation*

All partner institutions already provide the necessary infrastructure for the data/code management related to UPSIDE. This includes:

- software and processing power required to carry out the simulations;
- data storage during the project (institutionally managed servers);
- data archiving in public archives (TU Delft researchers can upload up to 1 TB of data to the 4TU.ResearchData per year free of charge, and Zenodo allows uploads of up to 50 GB each free-of-charge);

- data archiving for the data that will remain under closed access due to commercial reasons (institutionally managed servers).

Thus no costs have been considered regarding research data/code management services/infrastructure so far as we think that the capacity available for free options would be sufficient.

Regarding responsibilities, researchers in collaboration with the WP leaders will manage the data related to their respective WP (no need for a Data Manager or position alike).

5. Data Security

Address data recovery as well as secure storage and transfer of sensitive data

This chapter addressed data recovery as well as how secure storage and transfer of sensitive data will take place.

- During the project, researchers will be actively working on the data in work laptops/stations provided by the respective institution and remotely maintained by the respective ICT Department. Researchers will be encouraged to make master copies of sensitive data in institutional drives, accessed remotely via secure protocols (e.g., SFTP). This will ensure sensitive data is backed up on a daily basis following the respective institution's ICT security protocols.
- Data will be exchanged between partners via institutionally recommended file-sharing services (SURFDrive).
- For the development of code, researchers will be encouraged to use version control and remote repositories in institutional instances such as the TU Delft Gitlab, the DLR Gitlab, ABC.
- Public datasets will be published via the 4TU.ResearchData, Zenodo and GitHub where the data will be openly accessible to all.

In addition, the TU Delft Faculty Data Steward will provide additional advice, as needed, on data storage and process during the project.

6. Ethical aspects

To be covered in the context of the ethics review, ethics section of DoA and ethics deliverables. Include references and related technical aspects if not covered by the former.

Herewith included copy of the summary of Analysis of the Ethical dimension for ethics clearance of the Ethics summary report at proposal stage & status update M6.

The project aims to develop an Epidural Brain Interface (EBI) featuring a minimally invasive, high spatial resolution and multi-brain region stimulation and recording system as a Neuromodulation-based therapy (NT) for Treatment-Resistant Depression (TRD). The system will be validated in vivo in rat models of depression. The ethics issues raised relate to the use of animals, the potential use of human cells /tissues; the involvement of patients and clinicians in focus groups and interviews; and the potential transfer of personal data between the EU and the US.

6.1. Animals

6.1.1. *The rationale for using animals - Status update from UGhent and UF*

Many technological parameters of the *UPSIDE* device can and will be studied in vitro and in silico. The justified and ethical use of animals in experimental research is important as they provide data that we cannot obtain from human subjects. Animal data will contribute to our fundamental understanding of device, device handling/placement and neurostimulation methods and will serve to assess the efficacy and translational capacity of the *UPSIDE* system. Lastly, the information required to attain this project are unobtainable from non-invasive approaches.

Many technological parameters of the eFUS/eREC device will be studied in vitro and in silico. However, some of the tasks described in the DoA need to be investigated in experimental models using animals. Depression is a human disorder that involves the pathological/ dysfunctional regulation of mood and emotions, but these functions have identified biological substrates that are evolutionary conserved in mammals, and which validates the use of preclinical models. The justified and ethical use of animals in experimental research, especially in the area of psychiatric disorders, is important as they provide data that we cannot obtain from human subjects. One key anticipated outcome of *UPSIDE* will be the validation of an innovative new approach that represents a technological shift and improvement from what is available today. Animal data from *UPSIDE* will contribute to our fundamental understanding of neuroscience, and will serve to assess the translational value of eFUS for clinical applications in human subjects for targeted cases of neurological or psychiatric conditions.

Psychiatric disorders, including depression, are associated with changes in brain oscillations, and the identification of biomarkers is a component of our work. The eREC device will permit acute and chronic neurophysiological recordings from the control and the experimental model of depression providing brain network information unobtainable from non-invasive approaches. Invasive recordings in humans are rare and its more complicated to test new materials as we will do in our studies.

The rationale and the necessity for using animals has not changed since the beginning of the project.

6.1.2. *Planned experiments and animal numbers*

Data acquisition in animals will occur in WP2. Throughout the animal experimentation, care will be taken to apply the principles of the 3Rs, described in more detail below. An initial estimate of animals needed is listed in the DoA. Prior to using additional live animals, the numbers required will be decided following consultation with the Central Animalarium of the Faculty of Medicine, Ghent University.

In addition data acquisition in animals will occur in Work Packages 4 and 5 for biocompatibility, neurophysiological, and behavioural experiments. Throughout the animal experimentation in *UPSIDE*, care will be taken to apply the principles of the 3Rs as well, described in more detail below. Clinical depression presents more frequently in women compared to men, although this is often ignored in preclinical studies. We will use a balance of 50% male/female animals in all studies where a sex effect is predicted, including in behavioural, neurophysiological or other biological data. The sample numbers required will be decided following consultation with the Institute of Medical Biometry and Statistics (IMBI), Freiburg University.

Update on implementation M30

WP4 has been following the predetermined road map as described in the application. There are no changes in the number of animals used. The experiments to date have been carried according to EU-directive 2010/63/EU and the permissions accorded by the regional ethics committee (Regierungspräsidium Freiburg, TierSchG, G-23/080 for deliverables D4.1 (M18), D4.2 (M24), D4.3 (M27); and G-24/086 for deliverable D4.4 (M32)). A third permit is being prepared for deliverables D4.5 (M44) and D4.6 (M48). A systematic delay for the deliverables using the eFUS chip has been accorded by the EU (reason: delay in the production of the chip and the transfer to the Freiburg site).

6.1.3. The 3Rs: Reduction, Replacement, Refinement

Reduction: Power/ sample size calculations will be made given known variations in the expected outcome to have sufficient and as few as necessary animals in the groups. Stimulation parameters, and implantation methods will be optimized using in vitro methods or pilots before applying on the experimental groups. For each animal, multiple forms of data will be collected including neurophysiological data from chronic implants, broad-spectrum behavioural analysis, histological data after sacrifice of the animal. The approach is to maximise the amount of data that can be extracted from each animal, and so minimise the number of animals required to achieve the research objectives.

Replacement: As much as possible, protocols will be optimized in vitro, phantoms brains or using in silico models. However, the necessity to use animals has been argued above, and they play a key role in the preclinical validation process in which we are engaged. At the moment, we cannot conceive of any form of either scientific or technical advance that would yield similar clinically relevant information.

Refinement: The scientific protocols, animal welfare, the housing, enrichment, surgical procedures and post-operative care are the subject of continual discussion in terms of refinement and the establishment of best practices, in concert with our colleagues, ethical committees, and veterinarians. In the context of potential clinical applications, tasks in WP4 and 5 will be prepared following interaction with material scientists and the designers to optimize the device for chronic implantation and to minimize the histological impact.

Update on implementation M30

The WP2 and WP4's 3Rs strategies have not changed; no update to report on M30

6.2. Humans

Patients and clinicians will be involved in focus groups and interviews. While no information is provided in relation to recruitment and consent this does not raise any serious ethics issues and will have to be dealt with at local, institutional and project level to ensure compliance with EU regulations, therefore no requirements are stipulated.

The first focus group discussion between patients and the UPSIDE consortium will take place on March 19, 2025 in Freiburg. The protocol for the event is currently still being discussed and developed by UPSIDE members (Prof V Coenen, Dr M Döbrössy, L Ratz, Dr T Costa), UPSIDE Associate partners (Dr T Andreae and colleagues from the Focused Ultrasound Foundation), and members of the Psychiatry Department, Freiburg University (Prof JC Baldermann-Weiß, Prof T Schläpfer, Prof C Normann). A detailed description of the protocol and outcomes will be included in the final version of the project's DMP (D7.6) (M48) as well as in the final version of the project's C&D and Exploitation plan (D7.5) (M48).

6.3. Human cells/tissues

It is mentioned that cytotoxicity will be tested in primary cultures of astrocytes and neurons but no further details have been provided. If these are human cells project work will have to comply with Directive 2004 23 EC on human genetics and biological samples. This will be dealt with at local and institutional level, therefore no requirements are stipulated.

6.4. Non-EU countries

The USA partner is involved in networking and exploitation which will involve transfer of personal data from the EU to the US. As the applicant is obliged to ensure that all project work adheres to GDPR regulations this will be dealt with at project, local and institutional level, therefore no requirements are stipulated.

Status from FUSF M(6)

FUSF is committed anyhow to adhere to GDPR regulations. Therefore, no personal data will be shared by any means (e.g. subjects of clinical studies).

7. Other

Refer to other national/funder/sectorial/departmental procedures for data management that you are using (if any)

UPSIDE is committed to comply with the funder's research data management requirements of FAIR data, following the aim to publish as open as possible and as closed as necessary. Using that as a framework, the following policies regarding data/code management will also apply at the respective partner institutions:

TUD	<ul style="list-style-type: none">• TU Delft Research Data Framework policy: <p>The TU Delft Research Data Framework Policy expects researchers to ensure that research data, code and any other materials needed to reproduce research findings are appropriately documented and shared in a research data repository following the FAIR principles (Findable, Accessible, Interoperable and Reusable) for at least 10 years from the end of the research project unless there are valid reasons not to do so.</p> <ul style="list-style-type: none">• TU Delft Research Software policy• Netherlands Code of Conduct for Research Integrity (2018)Opens in a new window
UF	University Freiburg Medical Centre QM Policies

Table 7: In place policies for data management from partners

In addition, below brief some practical institutional procedures in place for data management.

7.1.1. TUD

TU Delft ICT department offers multiple options for secure storage of your data. In UPSIDE we are storing research data in “[Project Data \(U:\)](#)”. “Project drive” is a network drive which is backed up by TU Delft ICT. In addition, for data to be shared with UPSIDE partners, as described above *SURFdrive* and *Microsoft TEAMS* are facilitated for exchange of operational data streams. When it comes to sensitive data, or high sensitive IP/state sensitive data - additional measure (i.e. client side encryption) can be put in place. In addition, the data steward of the faculty of Micro-electronics is advising for the UPSIDE project based on actual needs the best legible solution for the data management.

7.1.2. UF

The UF Partners have strong activities in preclinical as well as clinical research in numerous fields, and have introduced GLP standards: the lab has developed a QM-Handbook defining critical and non-critical aspects of the daily routine in standard operation procedures, including form documents to ensure reproducible achievement of data. These documents are stored on the clinical computer server and access restricted to members of the department of stereotactic neurosurgery. In addition, main documents of the handbook are write-protected and change controlled by the QM representative. The electronic data storage is handled at main clinical level, including long-term preservation and back-up systems according to clinical regulations. The existing QM-Handbook is currently improved to reach true GLP standards, which not only will be limited to preclinical safety studies but also influence basic research where applicable. Research studies are defined using Test Plan documents, and results are electronically stored. Members are trained in the use of traditional lab books, and has computer storage space on the backed up clinical server. The GLP QM-Handbook is currently part of the regular external audits according to ISO 9001:2008.