SEVENTH FRAMEWORK PROGRAMME

INFORMATION AND COMMUNICATION TECHNOLOGIES

Project:

NoTremor- Virtual, Physiological and Computational Neuromuscular Models for the Predictive Treatment of Parkinson's disease

(NoTremor, Grant Agreement No. 610391)

NoTremor

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Executive Summary

This deliverable constitutes the Task 1.4 “Ethical issues” of Deliverable “D1.1 – Ethics Manual” of the NoTremor project (Grant Agreement No. 610391).

The Ethics Manual will specify which data are essential for the project and which should be excluded from retention. The manual will be used to scan all project partners’ deliverables and conduct. All relevant national and international European conventions will be fully integrated

This deliverable is a source of reference material for each of the partners. It ensures that all partners have knowledge of the initial test campaign strategy for the clinical assessments.

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List of abbreviations and acronyms

(*in alphabetic order*)

EAB	Ethics Advisory Board
ELSI	Ethical, Legal and Social Implications
DTA	Data Transfer Agreement
IP	Intellectual Property
RS-fMRI	Resting state functional Magnetic Resonance Imaging

Project description

NoTremor is a multidisciplinary translational project, drawing on data from previous and current Parkinson's research to develop patient-specific computational models that link midbrain degenerations to motor behaviour. These models will be tested in a clinical setting with a large cohort of PD patients in order to quantify and validate their ability to describe neural pathology effects on motor activity and to predict disease progression. The resulting tools for predictive simulation will assist both with clinical decision making – by improving the quality of analysis, prediction and progression of disease – and with virtual prototyping and testing of new drugs through the use of personalised virtual patient models.

Introduction

Tending to the ethical, legal and social implications (ELSI) of an interdisciplinary translational project such as NoTremor is necessarily a horizontal activity; it cuts across, informs and supports the various work packages.[1]

This ethics guidance is intended to serve as the basis for the monitoring work of the NoTremor Ethics Advisory Board (EAB). It is a practical guide through the established or anticipated areas of concern arising from tasks proposed, and takes as read the exclusions already detailed in the Description of Work.[2] The guidance details specific issues in each of three main areas of work: computer modelling, clinical trials, and dissemination/commercial exploitation. It notes relevant regulation and requirements, and suggests how issues may best be addressed. The guidance also outlines basic principles of research integrity, understood to apply to all working on this project.

The EAB is also responsible for reviewing and advising on other issues that may arise in the course of the project, which are either referred to them by project members or are elicited as part of work package reports or in the course of regulatory compliance. These can be added to this guidance document, thereby creating a comprehensive and coherent record of monitoring and advice.

[1] Description of Work B 1.3.2, Figure 7.

[2] As per Article 6 (2§) of Directive 1982/2006/EC, NoTremor does not engage in:

1. Research activity aiming at human cloning for reproductive purposes,

2. Research activity intended to modify the genetic heritage of human beings which could make such changes heritable,

3. Research activities intended to create human embryos solely for the purpose of research or for the purpose of stem cell procurement, including by means of somatic cell nuclear transfer.

Neither does it include any research involving the use of human embryonic tissue, human foetuses, human fetal tissue, other human tissues, genetic information, people unable to give consent, children pregnant women, nor animals.

General ethical considerations for NoTremor

Core ethical issues have been summarised in the Project "Description of Work" (DoW) B.4.2.2 as:

- Privacy protection and confidentiality.
- Informed consent.
- Incidental findings.
- Transparency of the collected data management by the final system and during its pilots.
- IT-Security and identity management.
- Risk assessment (Insurance).
- Delegation of control.
- Incentives (Financial inducements, etc.).

Specific ethical considerations for NoTremor areas of work

What follows spells out where and how these general ethical concerns arise in the three main areas of the project's work, with recommendations for how they be addressed.

1 Computer modelling

NoTremor aims to enhance computational models for PD by integrating and extending existing methods, frameworks and tools for neuro-musculo-skeletal modelling and model simulation (DoW B.1.1.2, Table 1).

1.1 Patient and participant data

Since this area of the project's work uses anonymised data and images from PD patients as inputs to aid development of models, it is model development, rather than the patient-related data, which is the focus of the research. This distinction means that the regulations specifically relating to human participation in research do not apply to this part of the project. The work and use of data is nevertheless subject to the European Directive on Data Protection and its national legislative iterations.[3]

- Ascertain whether participants are aware of and/or have given consent for use of images and data for research undertaken by third parties. If not, put appropriate notifications in place, namely:
    - specify third party information sharing in study protocol of data source;
    - consider seeking consent for third party use of anonymised data;
    - inform current project participants of the use of data specifically in NoTremor computer modelling.

[3] Directive 95/46/EC on the protection of individuals with regard to the processing of personal data and on the free movement of such data; UK Data Protection Act 1998; Hellenic Data Protection Authority.

1.1.1 Discussion

The protocol for the study undertaken as part of the Monument Discovery project, from which data is to be sourced, states:

"All data will be collected in a standard and uniform manner for entry into a central repository. This research database will be password protected, accessible only to the research team and hold anonymised information for each patient to ensure confidentiality."[4]

It is the case that, as long as no identifiable data is being processed without consent, there is no legal requirement for research governance or ethics approval of such a research database. The protocol does not, however, state what will be done with data, nor indicate that it will be shared with others.

Similarly with regard to future research use, the consent form for the study from which material will be sourced currently states only:

"I give consent for my tissues samples and my DNA to be used in possible future research by the research team into Parkinson's Disease." [5] (emphasis of limiting clauses added)

It is necessary to specify third party sharing in the protocol, and would be good practice to inform participants of this use. While it is not strictly necessary to obtain consent for use of anonymised data under the current EU Directive, it may soon be required under the European Data Protection Regulations that are to replace the Directive. [6] Addition of a clause regarding data would mirror the specificity of consent with regard to tissues and DNA.

Given that the researchers have a large and long-standing cohort with whom they are in fairly regular contact, it would be feasible and advisable to inform participants about the NoTremor project, and that anonymised data from the Monument Discovery project will feed into it. This is both a way to meet requirements of fair processing and a point of dissemination and participant engagement: people find it interesting to know how their material is being used. It provides a greater sense of the trajectory and/or life cycles of research and their contributions to this, and may in this instance also prepare the ground for the clinical trials/test campaigns part of the NoTremor project.

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[4] Protocol, "Understanding the early pathological pathways in Parkinson's Disease" Version 14: 14/10/2013, p 14.

[5] Participant Consent Form 2 "Understanding the early pathological pathways in Parkinson's Disease" Version 3: 03/12/2010, clause 3.

[6] See also No Tremor Description of Work B4.3.1 "…any conclusive needs within the project vis-à-vis the patient data. This may refer to the temporality for storage of data, security of data transfer and relevant consent applications and relevant advertisement of the use of the data."

1.2 Confidentiality and data security

The study protocol for the data source confirms that in order to ensure patient confidentiality, its research database is password protected, accessible only to the research team and holds linked-anonymised information.
The following conditions should be met for its transfer and use in NoTremor computer modelling:

- An appropriate data transfer agreement (DTA) is in place between the source study and its sponsor (University of Oxford) and the researchers and research institution receiving the material for NoTremor. This will specify:
  - Only anonymised images and characterising information are sent: any linking codes remain with the research team of the source study;
  - All material is encrypted before transfer;
  - All material held the NoTremor research site is password protected and accessible only by authorised study members;
  - Material may not be shared with other parties by the receiving site;
  - Other relevant conditions for length of storage and destruction.

1.3 Use of existing methods, frameworks and tools

- Provide evidence of agreements and permissions for use and extension of current software, where necessary.[7]

2. Clinical Trials: NoTremor 'Test campaigns'

Test campaigns in clinical research settings will afford opportunity to quantify and validate the ability of computer models to describe neural pathology effects on motor activity and to predict disease progression. Two test campaigns are proposed.
The first will:

- ground the model in experimental data
- quantify and fine tune the computational models and simulation framework developed with anonymised data (1, above)

The second will pilot three challenging applications of NoTremor:

- prediction and inverse estimation (clinical trial)
- simulated evaluation of established medicine (clinical trial)
- simulated evaluation of novel medicine

[7]Description of Work B.1.1.2; Annex 1 Letter of Support, Stanford University Schools of Medicine and Engineering

2.1 Patient participation – Test Campaigns

All but the final application of the second campaign – simulated evaluation of novel medicine – will involve participation of individuals with PD, under the auspices of three separate ethically approved research projects based in Oxford.

2.1.1 Discovery cohort (M Hu)

The already established cohort participating in the Monument Discovery project will be invited to participate in NoTremor test campaigns by means of additional tests or sub-studies to the current Discovery trial.

- All assessment tools and protocols to be used within NoTremor test campaigns will be verified in advance by the Ethics Advisory Board with a view to their impact to user's wellbeing.[8]
- All interventions and studies proposed will be integrated into the current ethically approved Discovery study, and evidence of approved amendment will be provided to the Ethics Advisory Board. Such an approach will:
  - Make it possible to deliver clinical data within the time constraints of NoTremor;
  - Make test campaigns proposed subject to the scrutiny of the Discovery study sponsor (University of Oxford) and the approving UK Research Ethics Committee.[9]

2.1.2 RS-fMRI (C Antoniades)

Eye movement recordings will be carried out on patients from the Discovery cohort as part of this separate research project.

- Review process for secondary recruitment of participants from Discovery project.
- Ensure that those recruited from this cohort have agreed to be invited to participate in other research.
- Ensure that the initial contact is made by researchers in the Discovery project on behalf of the Eye Movement study.
- Review Eye movement study documents and ethics approval.
- Ensure that the study includes sharing of information with other research projects, such as NoTremor. The considerations detailed at 1.1 will apply.

[8] As specified in Description of Work B.4.4.1.

[9] Such review will ensure that the test campaigns are undertaken in accordance with the Directive 2001/20/EC; Clinical Trials Directive of Implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use, including relevant jurisdictional provisions such as the Medicines for Human Use (Clinical Trials) Regulations 2004 and its amendments 2006a, 2006b, 2008 and 2009, UK Data Protection Act (1998) and, if samples are taken as part of the trials, the Human Tissue Act (2004).

2.1.3 Functional neurosurgery (P Brown)

- Review Functional neurosurgery study documents and ethics approval.
- Ensure the study includes sharing of information with other research projects, such as NoTremor. The considerations detailed at 1.1 will apply.

3. Dissemination and exploitation

The major focus of the NoTremor dissemination framework is to ensure that the project research and its practical outcomes are widely disseminated to the appropriate target communities, at appropriate times, via appropriate methods, and that those who can contribute to development, evaluation, uptake and exploitation of the NoTremor outcomes can be identified and encouraged to participate.

3.1 General considerations, applying also to focus groups and market analysis

- All NoTremor partners will use their industrial partnerships, standardisation activities and long-standing experience in EU funded projects to help dissemination, either through direct participation in WP7, or through their respective technical WP and activities.
- Communication of both the project research and its outcomes must be communicated clearly, in a manner appropriate to its audience, and in a way that neither overstates nor understates clinical outcomes and potential.
- Material on NoTremor and related websites, including information relating to the Discovery study, must be kept up to date.
- Appropriate consent and waivers will be obtained for promotional materials and videos that identify individuals.
- The manner in which the NoTremor framework is disseminated should always anticipate the different possible reactions. It is important that any project in this field does not, by its actions, degrade the wider public opinion of the novel techniques being created, which to some may be bordering on invasive or opening the doors to more loss of privacy.
- Exploitation arguments made in the project should take account both the needs for cost containment in the EU health system, the needs for Industry to make a profit and to realize that for most citizens, health care costs is a serious political social topic.

3.2 Publications, patents and other IP

- The Project Coordination Committee (PCC) should consider whether a project publication policy is required, and how publications, patents and other claims of intellectual property as set out in the Description of Work may be adjudicated.

4. Research integrity and the responsible conduct of research

The responsibility to ensure integrity and ethical practice in the conduct of research rests with individual researchers on the project. The Ethics Advisory Board will monitor observance and can act as arbitrating body in the case of uncertainties or conflicts that may arise in relation to research integrity.

Expectations of researchers in NoTremor include:

- Intellectual honesty in proposing, performing and reporting research. This includes the use of appropriate methods: reliable techniques and methods, appropriate statistical methods, no bias in results by choice of method.
- Accuracy in representing contributions to research proposals and reports.
- Collegiality in scientific interactions, including communications and sharing of resources. This includes clarifying ownership of data and attendant rights for publication.
- Adherence to the mutual responsibilities between investigators, research participants, and funding bodies.
- Transparency in conflicts of interest or potential conflicts of interest.
- Protection of human participants in the conduct of research.

5. Ethics Advisory Board

The NoTremor project will be assisted and advised by its Ethics Advisory Board (EAB).

The role of this board is to monitor and provide supervision and advice regarding ethical, legal and social aspects of the project, as well as good scientific conduct and research integrity. Its aim is to enhance the project and its standard of conduct by raising awareness of researchers of the ethical, legal and social issues present in or arising from their work, and by providing practical support and advice both to maintain regulatory compliance and to enact and further develop good practice in this area of research.

5.1 Terms of reference

- The board is a voluntary group with representation from multidisciplinary fields relevant to the three main areas of project work (computer modelling, clinical trials, and commercial exploitation) as well as a patient representative and an ethicist.

- All members of the board must provide a disclosure statement regarding their relationship(s) to any of the participating organisations in NoTremor, as well as any commercial interests.

- The EAB will convene regularly as an independent forum and representatives will also be invited to take part in Project Coordination Committee (PCC) meetings.

- Established or anticipated areas of concern and standards for both regulatory compliance and good practice are set out in the ethics manual, which will serve as a basis for the board's work. The EAB will ensure that requirements are met and standards are maintained by receiving and reviewing documents and protocols and recording any local regulatory approvals, such as those required by ethics committees.

- The EAB will also be responsible for reviewing and advising on other issues that may arise in the course of the project, which are either referred to them by project members or are elicited as part of work package reports or in the course of ensuring regulatory compliance.

- Although the EAB provides guidance and oversight and will assist with requests for advice, clarification and information, it remains the responsibility of individual project partners to keep informed about the legal and ethical regulations relevant to their own area of expertise in the NoTremor project, and to obtain any necessary local approvals. Similarly, the responsibility to ensure integrity and ethical practice in the conduct of research rests with individual researchers on the project. The EAB will monitor observance and can act as arbitrating body in the case of uncertainties or conflicts that may arise in relation to research integrity.

- All assessment tools and protocols to be used within NoTremor test campaigns will be reviewed in advance by the Ethics Advisory Board.

- Where appropriate, the EAB may contribute to ethics training of project partners, or take on other governance roles requested by the Project Coordination Committee (PCC).

- The EAB will report to the Project Coordination Committee and will refer any non-compliance, misconduct, or disregard of its advice to the PCC.

- Communication will be maintained between board members by a member's only distribution list. Communication with members of the NoTremor project will be through the normal channels established for project communication.

- Reports of the EAB will also be included in the periodic reports and in the final reports to the European Commission. It will report to the Project Coordination Committee by means of board meeting minutes and an annual report.

- The EAB will undertake an annual self-evaluation and will review, in particular, timelines for responding to items to be monitored as set out in the project ethics guidance as well as issues raised independently; quality and adequacy of responses.

- In the interests of transparency, the business of the EAB may be discussed outside of the board itself, unless there is explicit agreement that an item or issue is confidential. Minutes will be copied to the Project Coordination Committee and made available more widely on request.

- Public statements and any oral or written presentations on behalf of the EAB are to be corporate in nature, and distinguished from any representations made in a personal capacity.

5.2 Board composition and structure

Members of the board are drawn from project partners, including three recognized experts in the field, and augmented by lay members. Board members will include at least one individual representing each of the following:

- Computer Modelling
- Clinical Trials
- Commercial Exploitation
- Parkinson's Disease Patients
- Ethics and Governance

Although members may have expertise in more than one area or discipline designated, they may only be counted for purposes of membership as a representative of one area or discipline.

The board will be able to seek further expert advice on specific issues as proves necessary. Members will serve for the term of the three year project.